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Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease (Review)

Puhan MA, Gimeno-Santos E, Cates CJ, Troosters T

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[Intervention Review]

Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease

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ABSTRACT

Background

Guidelines have provided positive recommendations for pulmonary rehabilitation after exacerbations of chronic obstructive pulmonary disease (COPD), but recent studies indicate that postexacerbation rehabilitation may not always be effective in patients with unstable COPD.

Objectives

To assess effects of pulmonary rehabilitation after COPD exacerbations on hospital admissions (primary outcome) and other patient-important outcomes (mortality, health-related quality of life (HRQL) and exercise capacity).

Search methods

We identified studies through searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PEDro (Physiotherapy Evidence Database) and the Cochrane Airways Review Group Register of Trials. Searches were current as of 20 October 2015, and handsearches were run up to 5 April 2016.

Selection criteria

Randomised controlled trials (RCTs) comparing pulmonary rehabilitation of any duration after exacerbation of COPD versus conventional care. Pulmonary rehabilitation programmes had to include at least physical exercise (endurance or strength exercise, or both). We did not apply a criterion for the minimum number of exercise sessions a rehabilitation programme had to offer to be included in the review. Control groups received conventional community care without rehabilitation.

Data collection and analysis

We expected substantial heterogeneity across trials in terms of how extensive rehabilitation programmes were (i.e. in terms of number of completed exercise sessions; type, intensity and supervision of exercise training; and patient education), duration of follow-up (< 3 months vs ≥ 3 months) and risk of bias (generation of random sequence, concealment of random allocation and blinding); therefore, we performed subgroup analyses that were defined before we carried them out. We used standard methods expected by Cochrane in preparing this update, and we used GRADE for assessing the quality of evidence.

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Main results

For this update, we added 11 studies and included a total of 20 studies (1477 participants). Rehabilitation programmes showed great diversity in terms of exercise training (number of completed exercise sessions; type, intensity and supervision), patient education (from none to extensive self-management programmes) and how they were organised (within one setting, e.g. pulmonary rehabilitation, to across several settings, e.g. hospital, outpatient centre and home). In eight studies, participants completed extensive pulmonary rehabilitation, and in 12 studies, participants completed pulmonary rehabilitation ranging from not extensive to moderately extensive.

Eight studies involving 810 participants contributed data on hospital readmissions. Moderate-quality evidence indicates that pulmonary rehabilitation reduced hospital readmissions (pooled odds ratio (OR) 0.44, 95% confidence interval (CI) 0.21 to 0.91), but results were heterogenous (I^2 = 77%). Extensiveness of rehabilitation programmes and risk of bias may offer an explanation for the heterogeneity, but subgroup analyses were not statistically significant (P values for subgroup effects were between 0.07 and 0.11). Six studies including 670 participants contributed data on mortality. The quality of evidence was low, and the meta-analysis did not show a statistically significant effect of rehabilitation on mortality (pooled OR 0.68, 95% CI 0.28 to 1.67). Again, results were heterogenous (I^2 = 59%). Subgroup analyses showed statistically significant differences in subgroup effects between trials with more and less extensive rehabilitation programmes and between trials at low and high risk for bias, indicating possible explanations for the heterogeneity. Hospital readmissions and mortality studies newly included in this update showed, on average, significantly smaller effects of rehabilitation than were seen in earlier studies.

High-quality evidence suggests that pulmonary rehabilitation after an exacerbation improves health-related quality of life. The eight studies that used St George's Respiratory Questionnaire (SGRQ) reported a statistically significant effect on SGRQ total score, which was above the minimal important difference (MID) of four points (mean difference (MD) -7.80, 95% CI -12.12 to -3.47; I^2 = 64%). Investigators also noted statistically significant and important effects (greater than MID) for the impact and activities domains of the SGRQ. Effects were not statistically significant for the SGRQ symptoms domain. Again, all of these analyses showed heterogeneity, but most studies showed positive effects of pulmonary rehabilitation, some studies showed large effects and others smaller but statistically significant effects. Trials at high risk of bias because of lack of concealment of random allocation showed statistically significantly larger effects on the SGRQ than trials at low risk of bias. High-quality evidence shows that six-minute walk distance (6MWD) improved, on average, by 62 meters (95% CI 38 to 86; I^2 = 87%). Heterogeneity was driven particularly by differences between studies showing very large effects and studies showing smaller but statistically significant effects. For both health-related quality of life and exercise capacity, studies newly included in this update showed, on average, smaller effects of rehabilitation than were seen in earlier studies, but the overall results of this review have not changed to an important extent compared with results reported in the earlier version of this review.

Five studies involving 278 participants explicitly recorded adverse events, four studies reported no adverse events during rehabilitation programmes and one study reported one serious event.

Authors' conclusions

Overall, evidence of high quality shows moderate to large effects of rehabilitation on health-related quality of life and exercise capacity in patients with COPD after an exacerbation. Some recent studies showed no benefit of rehabilitation on hospital readmissions and mortality and introduced heterogeneity as compared with the last update of this review. Such heterogeneity of effects on hospital readmissions and mortality may be explained to some extent by the extensiveness of rehabilitation programmes and by the methodological quality of the included studies. Future researchers must investigate how the extent of rehabilitation programmes in terms of exercise sessions, self-management education and other components affects the outcomes, and how the organisation of such programmes within specific healthcare systems determines their effects after COPD exacerbations on hospital readmissions and mortality.

PLAIN LANGUAGE SUMMARY

Pulmonary rehabilitation for people who have been in hospital with an exacerbation of chronic obstructive pulmonary disease

Review question: We wished to compare the impact of pulmonary rehabilitation after an exacerbation of chronic obstructive pulmonary disease (COPD) on hospital readmissions and other patient-important outcomes such as quality of life versus usual post-exacerbation care.

Study characteristics: We included 20 studies involving 1477 participants with COPD. Rehabilitation programmes started in hospital in some trials and after discharge in others. These programmes showed great diversity in terms of exercise training (e.g. number of completed exercise sessions, type and intensity of exercise training), patient education (none to extensive self-management programmes) and how programmes were organised (within one setting, e.g. pulmonary rehabilitation, to across several settings, e.g. hospital, outpatient centre and home).

Key results: Quality of life and exercise capacity were improved by rehabilitation, and the effect was substantially larger than the minimal important difference. Results for hospital readmissions and mortality were diverse, with some studies showing that pulmonary rehabilitation reduced hospital admissions and mortality compared with usual community care (no rehabilitation), and other studies not showing such effects.

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Quality of the evidence: Uncertainty about reasons for differences across trials in terms of hospital readmissions and mortality led to downgrading of the quality of evidence (moderate-quality evidence for reduction in hospital readmissions and low-quality evidence for reduction in mortality). The quality of evidence was high for quality of life and exercise capacity.

Conclusion: Pulmonary rehabilitation improves quality of life and exercise capacity and is a safe intervention for patients with COPD after they have experienced an exacerbation. The reasons for diverse effects on hospital readmissions and mortality, however, are not fully clear. Future studies should explore whether the extent of the rehabilitation programme and the organisation of such programmes within specific healthcare systems (e.g. within the rehabilitation setting vs embedded in the continuum of care from hospital to home to outpatient care) determines the effects of rehabilitation after COPD exacerbations.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Pulmonary rehabilitation versus usual care

Pulmonary rehabilitation versus usual care for patients with COPD

Population: participants with COPD who had experienced a recent exacerbation
Setting: inpatient, outpatient or home-based
Intervention: rehabilitation
Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with rehabilitation				
Hospital readmission (to end of follow-up, median 9 months)	High risk for 1-year readmission		OR 0.44 (0.21 to 0.91)	810 (8 RCTs)	⊕⊕⊕⊖ Moderate[a]	
	500 per 1000	306 per 1000 (174 to 476)				
Mortality (to end of follow-up, median 12 months)	High risk for 1-year mortality		OR 0.68 (0.28 to 1.67)	670 (6 RCTs)	⊕⊕⊖⊖ Low[a,b]	None of the trials used mortality as a primary outcome, and none of the trials was powered to detect a meaningful effect of rehabilitation on mortality.
	150 per 1000	107 per 1000 (47 to 228)				
Health-related quality of life: St George's Respiratory Questionnaire - SGRQ: total score (to end of follow-up, median 5 months)	SGRQ score at beginning of rehabilitation was typically around 65	Mean change from baseline in SGRQ Total score in the intervention group was 7.80 units lower (95% CI -12.12 to -3.47)	-	1003 (8 RCTs)	⊕⊕⊕⊕ High[c]	A lower score indicates better quality of life.
Change from baseline in 6-minute walking test (to end of follow-up, median 3 months)	6-Minute walking distance at beginning of rehabilitation was typically around 300 metres	Mean change from baseline in 6-minute walking test in the intervention group was 62.38 metres more	-	819 (13 RCTs)	⊕⊕⊕⊕ High[d]	

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		(95% CI 38.45 to 86.31)		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; OR: odds ratio; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded because of heterogeneity of treatment effects with unclear reasons.
[b]Downgraded because of large 95% CI crossing 1.0.
[c]Statistical testing of heterogeneity showed significant differences in results across trials, but we did not downgrade the quality because the heterogeneity does not affect interpretation of results. Studies did not have an active control, and participants were aware of group assignment, but we did not downgrade because this did not lower our confidence in the estimate of effect.
[d]Unexplained substantial statistical heterogeneity detected (I^2 = 87%), but we did not downgrade the quality because the pooled effect is large and well above the minimal important difference for the 6-minute walking test of 30 metres.

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BACKGROUND

Clinical guidelines and documents of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) include positive recommendations for pulmonary rehabilitation after chronic obstructive pulmonary disease (COPD) exacerbations based on earlier versions of this systematic review and its included trials (BTS 2013; ERS ATS Statement 2013; GOLD 2016). However, recent studies indicate that post exacerbation rehabilitation may not always be effective. In addition, concerns have arisen that pulmonary rehabilitation may not be safe shortly after exacerbations of COPD. Therefore, our aim is to update our previous systematic review by assessing the effectiveness and safety of pulmonary rehabilitation after exacerbations of COPD.

The protocol for this Cochrane review was based on a previously published non-Cochrane systematic review (Puhan 2005).

Description of the condition

Exacerbations and hospitalisations in patients with COPD represent a major health burden for both patients and healthcare systems in industrialised and developing countries (Chan-Yeung 2004; Kessler 2006; Seemungal 1998; Sin 2002; Sullivan 2000). Acute exacerbations are the most common reason for hospital admissions and death among patients with COPD (Aaron 2014; Garcia-Aymerich 2003; Mannino 2002; Piquet 2013; Soler-Cataluna 2005). In addition, patients with COPD have reported reduced health-related quality of life (HRQL) (Kessler 2006; Schlenk 1998) compared with the healthy population, which is further impaired by acute and repeated exacerbations (Seemungal 1998). Patients are at risk of early death and continued exacerbations requiring hospitalisation (Aaron 2014; Piquet 2013; Soler-Cataluna 2005). Mortality rates during the year following a hospitalisation are around 35% (Almagro 2002; Connors 1996; Groenewegen 2003; Seneff 1995; Vitacca 2001), and rehospitalisation rates are around 60% (Connors 1996; Cydulka 1997; Escarrabill 2014; Groenewegen 2003; Martin 1982).

From the healthcare provider's perspective, COPD is resource-consuming (Ford 2015; Jansson 2013; Sullivan 2000). Acute exacerbations are the cost drivers for COPD care, accounting for more than 70% of COPD-related costs incurred as the result of emergency visits and hospitalisations (NHLBI 2001; Oostenbrink 2004; Sullivan 2000).

Description of the intervention

Position papers of the American College of Physicians, the American College of Chest Physicians, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the National Institute for Health and Care Excellence (NICE) have provided recommendations on acute care and follow-up management for acute exacerbations (Amir 2011; GOLD 2016; NICE 2010). Pulmonary rehabilitation could play an important role in peri-exacerbation management (management around the time of an exacerbation) because it combines several interventions that are known to improve health status and prognosis, such as physical exercise, smoking cessation, self-management education, optimisation of medications and psychological and social support (BTS 2013; ERS ATS Statement 2013; Maddocks 2015; Puhan 2014). A large body of evidence on patients with stable COPD shows that pulmonary rehabilitation improves exercise capacity and HRQL (McCarthy 2015), and that it may be cost-effective (ERS ATS Statement 2013; Griffiths 2001).

How the intervention might work

A multi-disciplinary approach to pulmonary rehabilitation addresses multiple risk factors for hospital readmission and determinants of poor exercise capacity and quality of life. This combined effect may accelerate recovery from exacerbations and lower the risk of hospital readmission by improving exercise capacity, alleviating symptoms and promoting better self-management.

Why it is important to do this review

COPD exacerbations are a major burden for patients, caregivers and society. Evaluation of the effectiveness and safety of post exacerbation strategies such as pulmonary rehabilitation could substantially lower the disease burden.

OBJECTIVES

To assess effects of pulmonary rehabilitation after COPD exacerbations on hospital admissions (primary outcome) and other patient-important outcomes (mortality, HRQL and exercise capacity).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing pulmonary rehabilitation with conventional community care after acute exacerbations of COPD. We included studies reported as full text, those published as abstract only and unpublished data.

Types of participants

Participants with COPD after inpatient or outpatient care for acute exacerbation. This review required that more than 90% of study participants were patients with COPD.

Types of interventions

Any inpatient and/or outpatient pulmonary rehabilitation programme, including at least physical exercise (endurance or strength exercise, or both), delivered to patients who have received acute care for an exacerbation of COPD. The rehabilitation programme must commence immediately after initiation of exacerbation treatment or within three weeks of initiation of exacerbation treatment. We did not apply a criterion for the minimum number of exercise sessions to be included in the review because guideline recommendations provide no definition for when a programme qualifies as rehabilitation based on the number or type of exercise sessions. Rehabilitation programmes could include additional components such as self-management education, psychological support, dietary advice and breathing exercises. We excluded from the review studies on pulmonary rehabilitation programmes that included only neuromuscular stimulation or inspiratory muscle training but no physical exercise programme. We included usual care control groups.

Types of outcome measures

Primary outcomes

- Hospital admissions (at least one hospital admission during follow-up)

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Secondary outcomes

- HRQL as measured by generic (e.g. Short Form (SF)-36) or disease-specific questionnaires (e.g. Chronic Respiratory Questionnaire (CRQ), St George's Respiratory Questionnaire (SGRQ))
- Exacerbation rates (after discharge)
- Number of outpatient visits
- Length of readmissions
- Mortality
- Functional exercise capacity as measured by two-, three-, four-, six- or 12-minute-walk test, or by a shuttle walk test
- Maximal exercise capacity
- Exercise endurance
- Withdrawals
- Adverse events
- Costs

Search methods for identification of studies

Electronic searches

We detailed in Appendix 1 search methods used in the previous version of this review. The previously published version included searches up to March 2010. The search period for this update is March 2010 to October 2015.

For this update, we identified trials from the Cochrane Airways Review Group Specialised Register (CAGR), which is maintained by the Information Specialist for the Group. This Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, and by handsearching of respiratory journals and meeting abstracts (see Appendix 2 for details). We searched all records in the CAGR using the search strategy presented in Appendix 3.

We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/). We searched all databases from their inception to October 2015, with no restriction on language of publication. We screened the list of papers on pulmonary rehabilitation that is prepared bimonthly by the Rehabilitation and Chronic Care Group of the European Respiratory Society (ERS) and sent to its members (MP). We completed handsearching on 5 April 2016.

Searching other resources

We screened reference lists from included primary studies, review articles and conference proceedings of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) (ERS ATS Statement 2013), and we contacted experts in the field to ask about additional published and unpublished studies. We applied no restrictions on the language of articles and completed handsearching on 5 April 2016.

Data collection and analysis

Selection of studies

Three review authors/contributors (MP, EGS, MS) independently assessed the titles and abstracts of all identified citations. Review authors recorded and then compared decisions (to order full-text article or reject). We resolved disagreements by consensus with close attention to the inclusion/exclusion criteria. Three review authors/contributors (MP, EGS, MS) evaluated the full text of all potentially eligible papers and made a decision whether to include or exclude each study according to the inclusion and exclusion criteria specified above. We again resolved disagreements by consensus with close attention to the inclusion/exclusion criteria. We excluded all studies that did not fulfil all of the criteria and listed their bibliographic details, along with reasons for exclusion. A third review author (CC or TT) resolved discrepancies if two review authors disagreed.

Data extraction and management

Three independent review authors/contributors (MP, EGS, MS) independently screened the full texts of included studies and recorded details about study design, interventions, participants and outcome measures in a predefined Windows Excel form. We tested the data collection forms on a small sample of studies with strong likelihood for inclusion and exclusion. A third review author resolved disagreements. We registered bibliographic details such as study author, journal, year of publication and language.

Assessment of risk of bias in included studies

We assessed risk of bias in included studies as high, low or unclear using the Cochrane 'Risk of bias' tool (Higgins 2011) and the following risk types.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We recorded the initial degree of discordance between review authors and corrected discordant scores based on obvious errors. We resolved discordant scores based on real differences in interpretation through consensus or third party arbitration. Review authors were not blinded to names of study authors, institutions or journals nor to trial outcomes.

Measures of treatment effect

When possible, estimates and confidence limits were related to the minimal important difference (MID) (Schunemann 2005) for each outcome. We assessed whether estimates and 95% confidence limits for differences between study groups exceeded the MID (Chronic Respiratory Questionnaire ± 0.5 on seven-point scales and St George's Respiratory Questionnaire ± 4 points; Schunemann 2003) or represented an important effect (six-minute walk distance ≥ 30 meters, which is based on a broad consensus and is less than the previous definition, and incremental shuttle walk test ≥ 47.5 meters; Holland 2014; Singh 2014).

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Unit of analysis issues

The unit of analysis was the participant. We neither encountered nor expected any non-standard study designs.

Dealing with missing data

We contacted study authors to obtain missing information.

Assessment of heterogeneity

We used forest plots to compare results across trials and the I^2 statistic to measure heterogeneity among them. When we identified substantial heterogeneity, we reported this and explored possible causes by performing prespecified subgroup analyses (extent of rehabilitation programme, length of follow-up (< 3 months vs ≥ 3 months)) and by analysing methodological items derived from the quality assessment (generation of random sequence, concealment of random allocation and blinding (low risk vs unclear or high risk). Previous versions of this review used length of follow-up and methodological items (Puhan 2011). Compared with earlier versions of this review, investigators created extent of rehabilitation programmes as a new explanatory variable for heterogeneity (see below) on the basis of recent discussions (Hopkinson 2014; Maddocks 2015; Spruit 2014) and before meta-analyses were carried out.

Pulmonary rehabilitation programmes can differ in many aspects, which may influence their effectiveness. Such programmes take place in inpatient, outpatient or home-based settings; are of short (e.g. six weeks) or long (e.g. six months) duration and involve different intensity (e.g. training twice per week, daily training). Exercise training can include both endurance and strength training or either of the two. and many types of exercise training can be chosen to match the needs of patients. Pulmonary rehabilitation programmes also differ in terms of patient education offered, from basic advice to extensive self-management programmes. Finally, adherence to a pulmonary rehabilitation programme determines the amount of training and education actually received by participants (e.g. attendance at 60% of planned exercise sessions).

Given the increasing diversity of pulmonary rehabilitation programmes and various ways to implement them in real-world practice, we introduced a new reason to explain heterogeneity as part of the update of this systematic review. We assessed how extensive rehabilitation programmes were as a possible source of heterogeneity of trial results, and we stratified meta-analyses by studies that offered an extensive pulmonary rehabilitation programme and studies that offered only moderately, slightly or not extensive pulmonary rehabilitation programmes (summarised as "less extensive" rehabilitation programmes). Review authors developed and used an approach not used before for assessment of the extent of rehabilitation programmes. When possible, we followed the statements and guidelines of national (British Thoracic Society; BTS 2013) and international societies (ERS and American Thoracic Society (ATS); ERS ATS Statement 2013). We did not upgrade or downgrade the extent of rehabilitation programmes if programme characteristics were in line with these statements and guidelines, but we downgraded or upgraded, respectively, the extent of programmes if some components were less than or exceeded what these guidance documents recommend. We considered pulmonary rehabilitation programmes to be extensive if:

- participants followed, on average, at least 16 exercise training sessions, calculated as the total number of possible exercise training sessions times the (average) attendance rate. For example, if a programme was designed to include at least five exercise training sessions in the hospital, followed by a standard eight-week outpatient programme with three sessions per week, 5 + 24 = 29 sessions were possible. If the attendance rate was 80%, participants followed, on average, 23 exercise training sessions. We selected a cut-off of 16 exercise sessions based on duration of outpatient programmes of at least eight weeks, with two to three sessions per week and an attendance rate of 80% (thus 8*2.5 - 4 = 16 sessions), as recommended by ERS and ATS (ERS ATS Statement 2013), rather than on the lower minimum number of sessions (≥ 12) recommended by BTS (BTS 2013);
- they included two to three exercise training sessions per week, as recommended by ERS, ATS and BTS (ERS ATS Statement 2013, BTS 2013);
- exercise training included at least endurance exercise (± strength exercise), as recommended by ERS, ATS and BTS (ERS ATS Statement 2013, BTS 2013); or
- most exercise training sessions were supervised by physiotherapists or other trained health professionals, as recommended by ERS, ATS and BTS (ERS ATS Statement 2013, BTS 2013).

Similar to the GRADE approach, we downgraded the extent of pulmonary rehabilitation programmes for the following reasons (e.g. by -1 from extensive to moderately extensive).

- By -1 if the total number of exercise training sessions was between 10 and 15, and by -2 if the total number of exercise training sessions was less than 10.
- By -1 if fewer than 2 training sessions were provided per week.
- By -1 if training was offered that is unlikely to modify the risk for hospital admissions and mortality, and is unlikely to improve health-related quality of life and exercise capacity (e.g. only outdoor walking without the use of tests or parameters that would ensure training of at least moderate intensity, only strength exercise, less than 20 minutes of endurance training per session, other reasons).
- By -1 if most exercise training sessions were not supervised by physiotherapists or other trained health professionals, and by -2 if most exercise training sessions (> 80%) were not supervised at all.

We upgraded the extent of pulmonary rehabilitation programmes for the following reasons.

- By +1 if the total number of exercise training sessions was greater than 30.
- By +1 if pulmonary rehabilitation programmes included an extensive self-management programme (i.e. patient education about COPD, self-monitoring, early action when exacerbations develop, written action plan, etc.).

Two review authors (EGS and MP) independently graded the pulmonary rehabilitation programmes of all included trials and resolved discrepancies in grading by discussion. If discrepancies remained, a third review author made the final decision.

Finally, we assessed how results changed with the addition of new studies and stratified analyses by studies included in the earlier version of this review versus studies added in this update.

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Assessment of reporting biases

When we were able to pool more than 10 studies, we created and examined a funnel plot to explore possible small study and publication biases.

Data synthesis

We pooled trial results by calculating mean differences (MDs) and pooled odds ratios (ORs) using random-effects models in Review Manager 5 (RevMan 2014).

'Summary of findings' table

We included a 'Summary of findings' table for the 2016 update of the review. We selected the following outcomes in consultation with the Cochrane Airways Review Group editorial team: hospital readmissions, mortality, SGRQ total score and six-minute walk test.

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to studies that contributed data to the meta-analyses for prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) along with GRADEpro software (December 2015 version). We justified all decisions to downgrade or upgrade the quality of studies by using footnotes and made comments to aid the reader's understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

We performed prespecified subgroup analyses when extent of the rehabilitation programme (extensive vs less extensive), length of follow-up (< 3 months vs ≥ 3 months) and methodological items from the quality assessment (generation of random sequence, concealment of random allocation and blinding (low risk vs unclear or high risk) served as stratification variables (see Assessment of heterogeneity for details).

We used the formal test for subgroup interactions provided in Review Manager 5.3 (RevMan 2014).

Sensitivity analysis

We considered using a fixed-effect model for sensitivity analyses but, given the heterogeneity of results across studies, we decided to use only a random-effects model.

RESULTS

Description of studies

Results of the search

In the original search, we identified 1759 citations through searches of electronic databases. We excluded 1740 citations after screening titles and abstracts and retrieved a total of 22 studies for detailed evaluation (19 obtained through searches of electronic databases and three via handsearching). We included six reports in the original review (Behnke 2000; Kirsten 1998; Man 2004; Murphy 2005; Nava 1998; Troosters 2002).

The search for the first update covered the period from July 2008 to March 2010. We identified 62 references through the electronic database search. We retrieved for full-text assessment three articles from electronic databases and one via handsearching. We included three additional references (Carr 2009; Eaton 2009; Seymour 2010) in the review update.

The search for the most recent and current update covered the period from April 2010 to October 2015, with handsearches run to 5 April 2016. We identified 449 references through the electronic database search. We retrieved for full-text assessment 20 references from electronic databases and two via handsearching. Figure 1 shows a study flow diagram. We included 11 additional studies (Borges 2014; Deepak 2014; Greening 2014; He 2015; Ko 2011; Tang 2012; Torres-Sánchez 2014; Torres-Sánchez 2015; Troosters 2010; Ko 2016; Liao 2015) in this review update.

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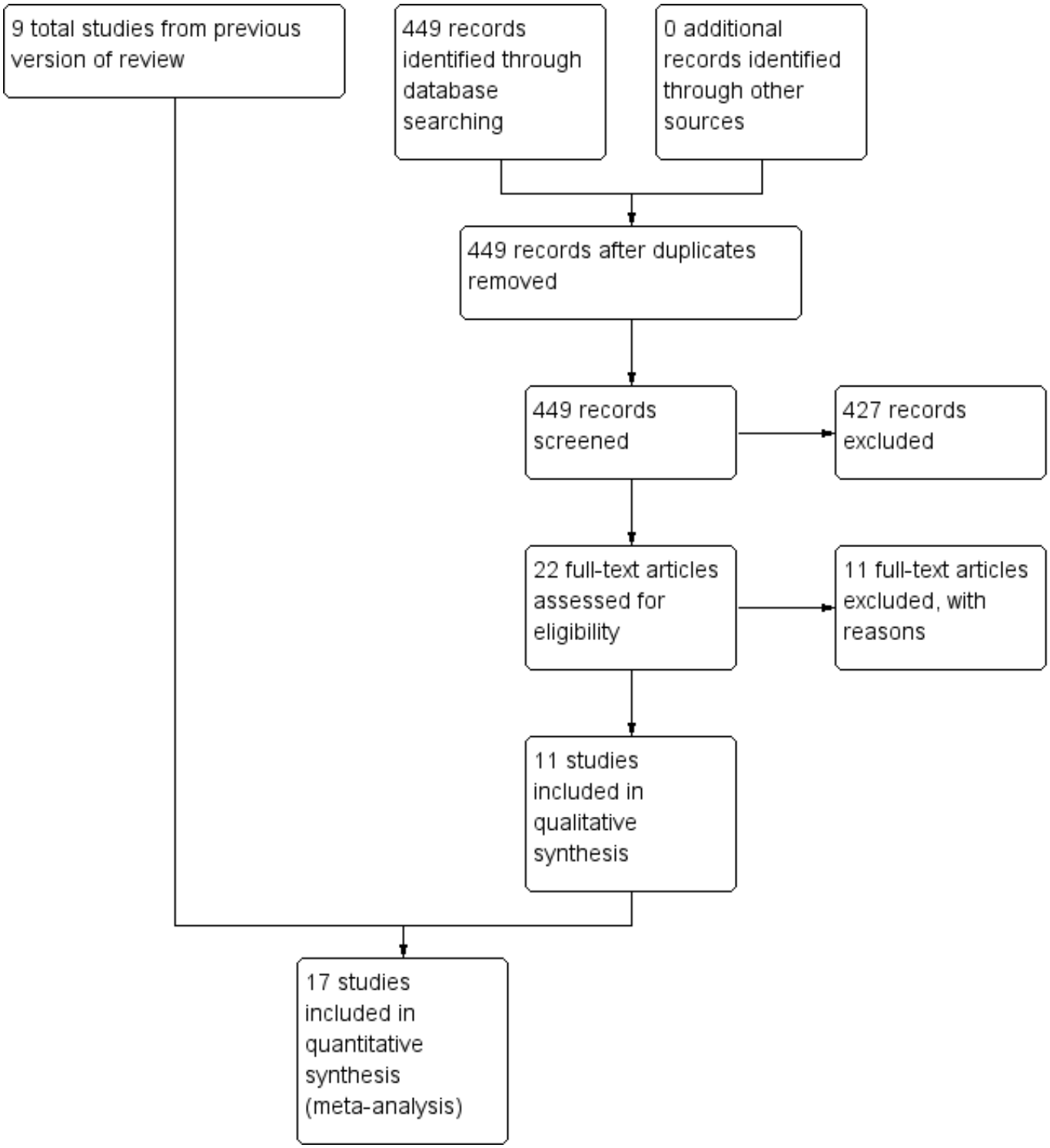
Figure 1. Study flow diagram.



Included studies

Twenty studies (drawn from 22 citations) met the eligibility criteria of this review. Eighteen studies were published in peer-reviewed journals, one study as an abstract (Torres-Sánchez 2014) and one as an abstract and as part of a full publication (Troosters 2002). The studies involved a total of 1477 participants who were in the recovery phase of a recent COPD exacerbation. Greening 2014 involved people with different respiratory conditions, however we were able to include the ITT data from COPD patients only; these data were provided to us by the authors upon request.

In 12 studies (Behnke 2000; Borges 2014; Eaton 2009; Greening 2014; He 2015; Kirsten 1998; Liao 2015; Nava 1998; Tang 2012; Torres-Sánchez 2014; Torres-Sánchez 2015; Troosters 2010), partic-

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ipants started inpatient pulmonary rehabilitation within two to eight days of hospital admission; in one study (Carr 2009), participants started an inpatient or outpatient rehabilitation programme; in six studies (Deepak 2014; Ko 2011; Ko 2016; Man 2004; Seymour 2010; Troosters 2002), outpatient rehabilitation was initiated after inpatient exacerbation treatment; and in one study (Murphy 2005), outpatient rehabilitation was started after "home from hospital care programme" for the exacerbation. Thirteen studies reported rehabilitation programme completion rates ranging from 40% to 94% (median, 77%). Only one study (Troosters 2010) provided details about the exacerbation treatment provided to participants (i.e. 32 mg oral corticosteroids for one week). For eight studies, we found that participants followed extensive pulmonary rehabilitation (Behnke 2000; Man 2004; Ko 2011; Ko 2016; He 2015; Nava 1998; Seymour 2010; Troosters 2002), and in seven studies, they completed moderately extensive pulmonary rehabilitation (Carr 2009; Eaton 2009; Greening 2014; Kirsten 1998; Liao 2015; Murphy 2005; Torres-Sánchez 2015), whereas participants followed slightly extensive pulmonary rehabilitation in one study (Tang 2012) and pulmonary rehabilitation that was not extensive in two studies (Borges 2014; Troosters 2010). For two studies, we could not determine the extensiveness of the pulmonary rehabilitation programme (Deepak 2014; Torres-Sánchez 2014). See Assessment of heterogeneity and Characteristics of included studies for details of the assessment of each included study (Table 1).

Excluded studies

The main reason for study exclusion was that the study population did not have COPD. We recorded reasons for exclusion of 10 studies in the Characteristics of excluded studies table.

Risk of bias in included studies

For details about risk of bias judgements and an overview of judgements across studies, see the Characteristics of included studies tables (Figure 2).

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Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

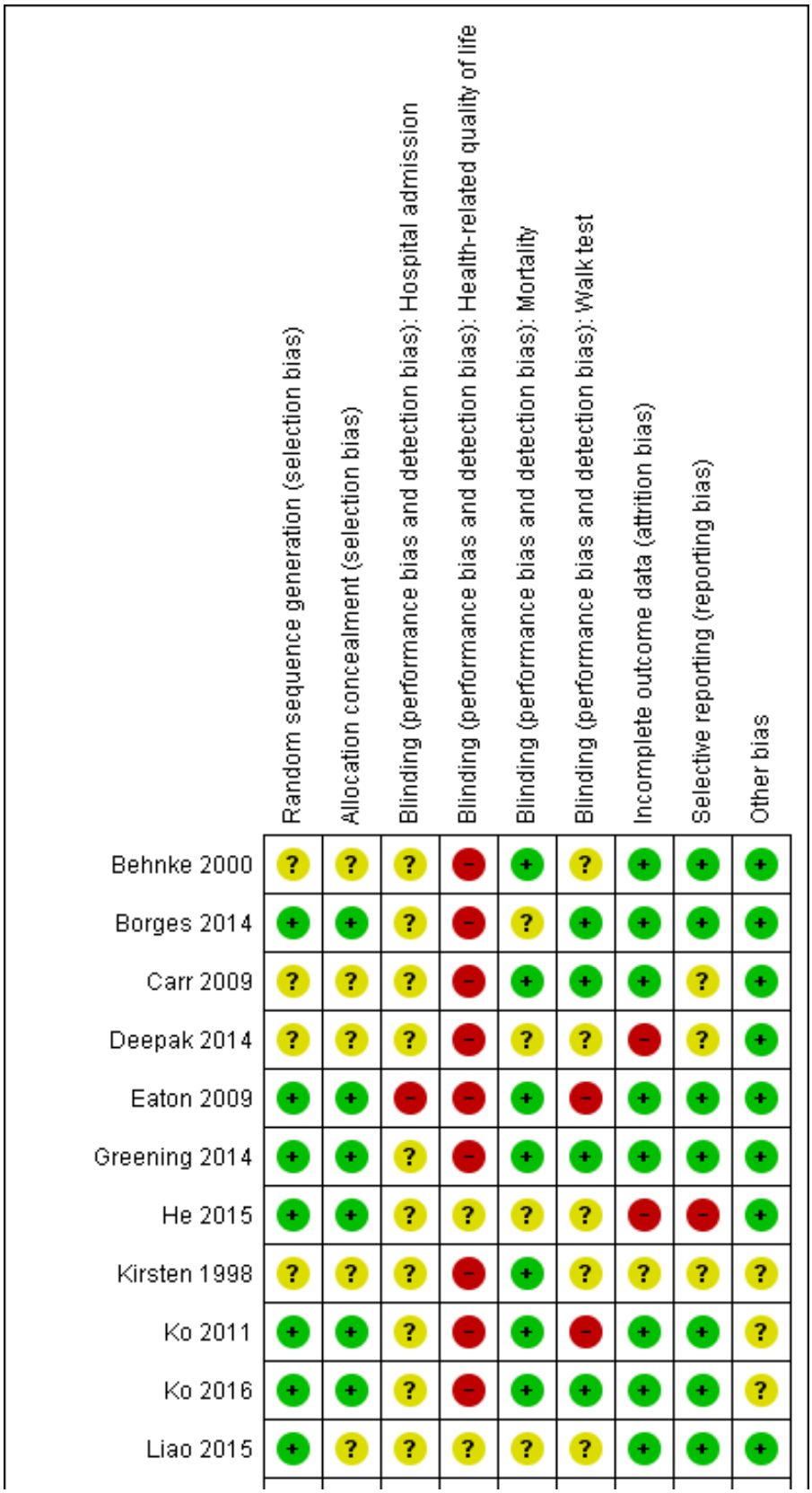

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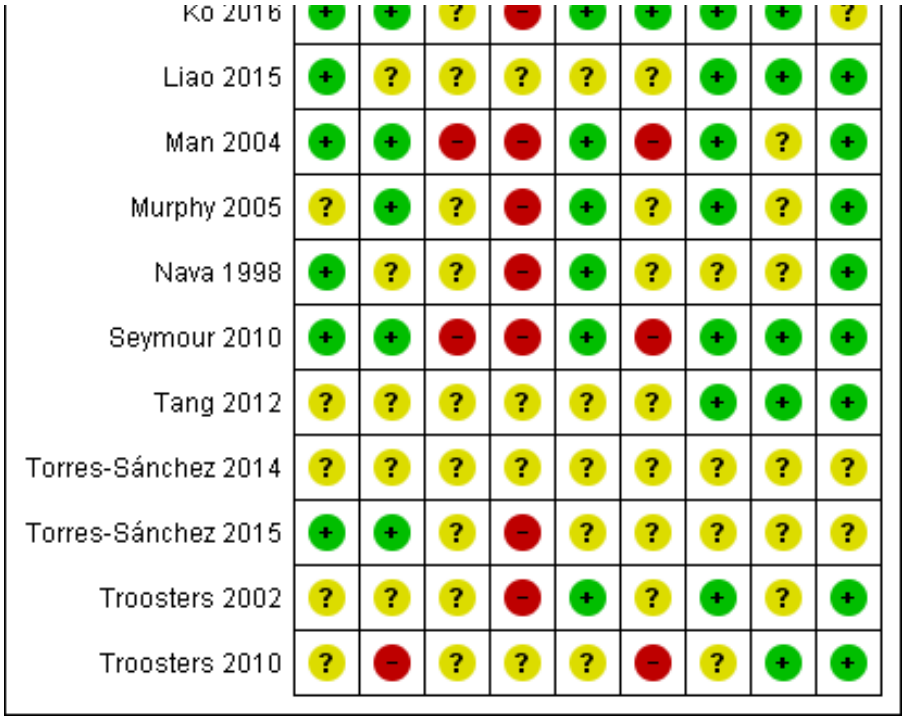
Figure 2. (Continued)



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Allocation

When reported, available information regarding treatment group assignment and allocation concealment indicated low risk of bias.

Blinding

Participants could not be blinded in these studies; this fact may have introduced bias for outcomes such as health-related quality of life, but it is less likely to be an important source of bias for mortality and hospital readmission. Outcome assessors could be blinded for outcomes such as exercise endurance or six-minute walk distance, and three studies described such blinding (Borges 2014; Carr 2009; Greening 2014).

Incomplete outcome data

Some studies did not assess the outcomes of participants who dropped out of rehabilitation programmes or were lost to follow-up. However, reported study flows suggest that the extent of attrition bias is likely to be small.

Selective reporting

We found no evidence of reporting bias.

Other potential sources of bias

We identified no other potential sources of bias. We did not create a funnel plot for the primary outcome, as fewer than 10 studies contributed to this outcome.

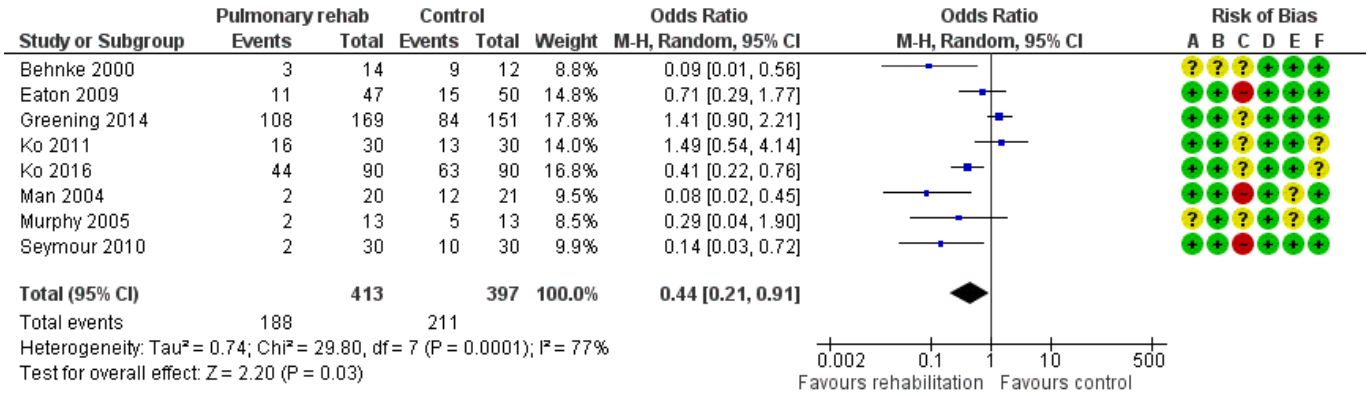
Effects of interventions

See: **Summary of findings for the main comparison** Pulmonary rehabilitation versus usual care

Hospital readmissions

Eight studies involving 810 participants (Behnke 2000; Eaton 2009; Greening 2014; Ko 2011; Ko 2016; Man 2004; Murphy 2005; Seymour 2010) contributed data on hospital readmissions. The follow-up period for these studies ranged from three to 18 months, with a median duration of nine months. Moderate-quality evidence (Summary of findings for the main comparison) shows that pulmonary rehabilitation reduced hospital readmission (pooled odds ratio (OR) 0.44, 95% confidence interval (CI) 0.21 to 0.91; Figure 3). However, the results were heterogenous (I^2 = 77%), with four studies showing large and statistically significant reductions in the risk of hospital admission associated with pulmonary rehabilitation, and four studies showing no effect. Although subgroup analyses performed to investigate heterogeneity showed no statistical significance (P < 0.05), extensiveness of rehabilitation programmes and methodological quality may explain heterogeneity, and length of follow-up may not (Analysis 1.7; Analysis 1.8; Analysis 1.9; Analysis 1.10; Analysis 1.11). Figure 4 shows that studies newly included in this update reported, on average, smaller effects of rehabilitation than were noted in earlier studies.

Figure 3. Forest plot of comparison: 1 Rehabilitation versus control, outcome: 1.1 Hospital readmission (to end of follow-up).



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias): Hospital admission
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

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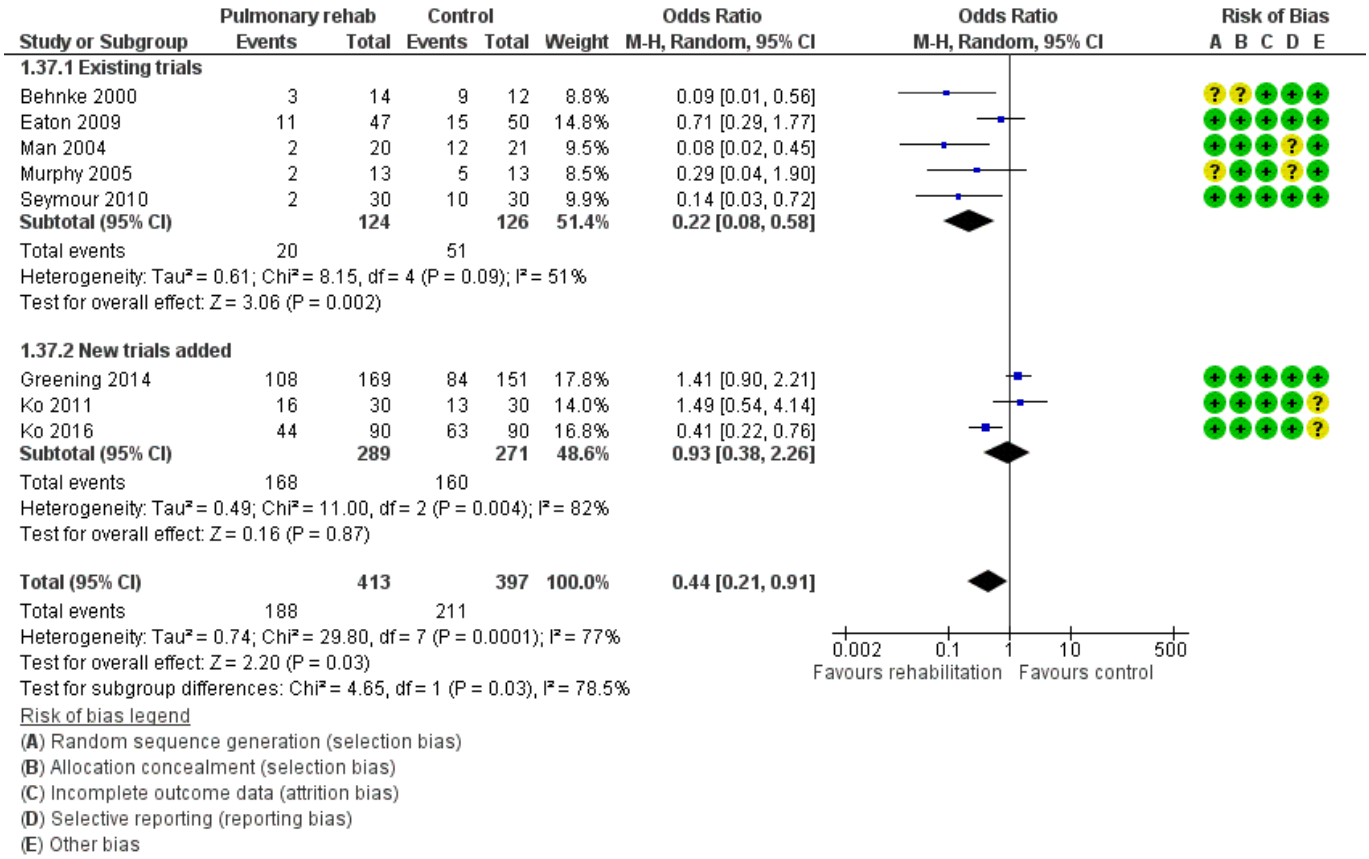
Figure 4. Forest plot of comparison: 1 Rehabilitation versus control, outcome: 1.37 Hospital readmission (to end of follow-up) with separated new trial data.



Mortality

Six studies including 670 participants contributed data on mortality (Behnke 2000; Greening 2014; Ko 2011; Ko 2016; Man 2004; Troosters 2002). The follow-up period for these studies ranged from three to 48 months, with a median duration of 12 months. The quality of evidence was low (Summary of findings for the main comparison), and meta-analysis showed no statistically significant effects of rehabilitation on mortality (pooled OR 0.68, 95% CI 0.28 to 1.67; Figure 5). Again, results were heterogenous (I^2 = 59%), with one study showing reduced mortality, one study excessive mortality and four no effect. Subgroup analyses showed statistically significant differences in subgroup effects between studies with more and less extensive rehabilitation programmes (Analysis 1.12) and between studies at low and high risk of bias (Analysis 1.14; Analysis 1.15), suggesting explanations for the heterogeneity, but length of follow-up did not explain heterogeneity (Analysis 1.13). As for hospital readmissions, Figure 6 shows that studies newly included in this update reported, on average, smaller effects of rehabilitation on mortality than were noted in earlier studies.

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Figure 5. Forest plot of comparison: 1 Rehabilitation versus control, outcome: 1.2 Mortality.

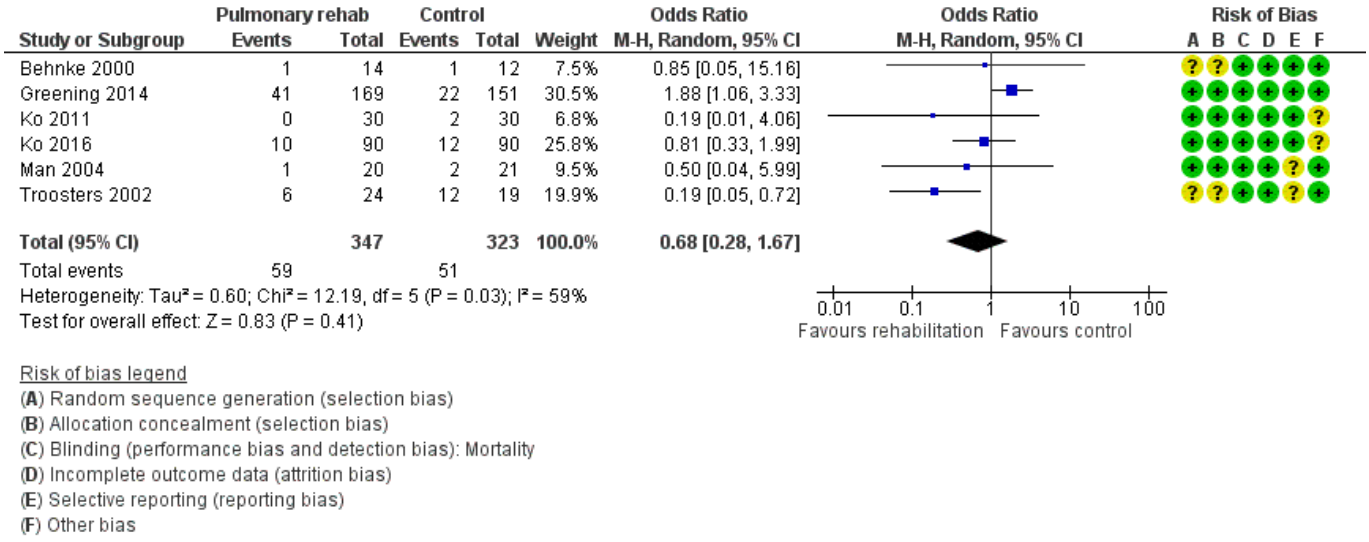
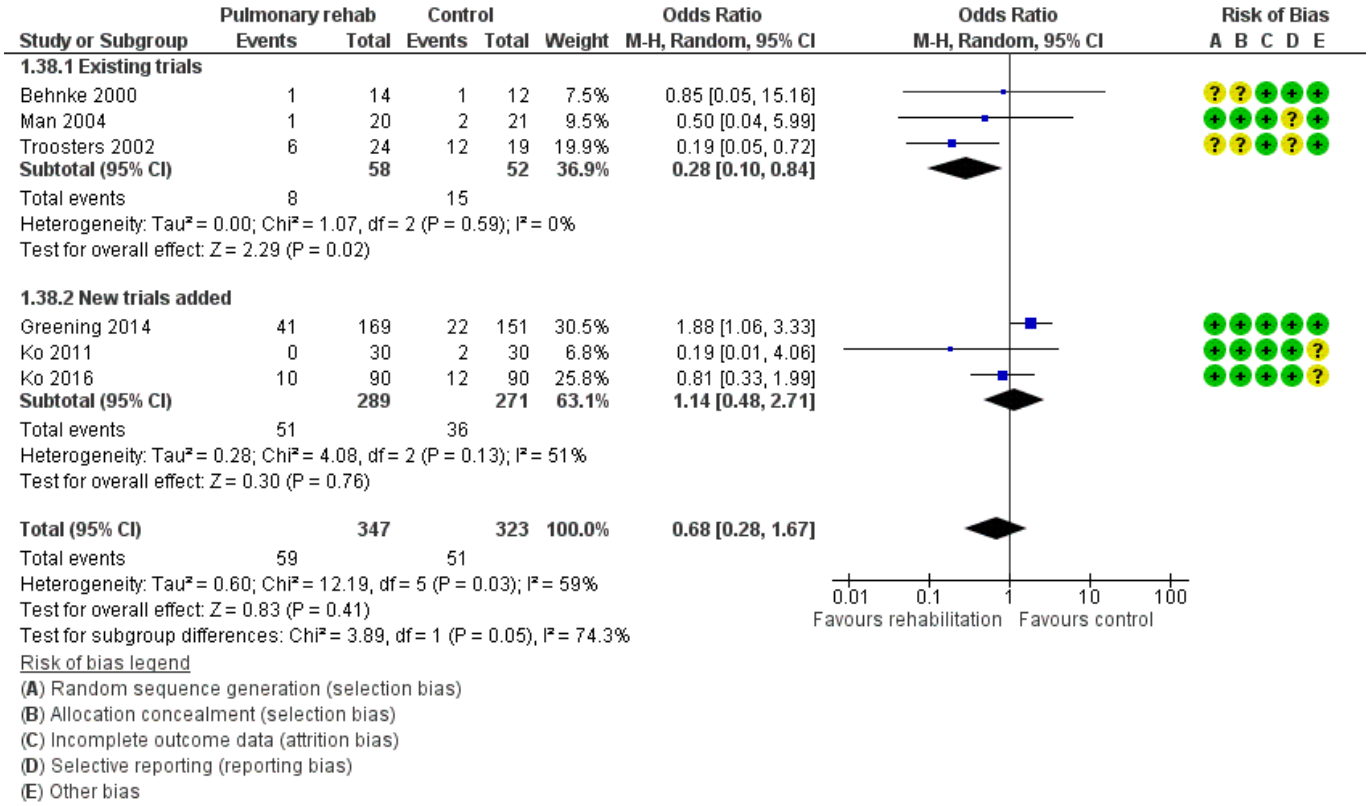


Figure 6. Forest plot of comparison: 1 Rehabilitation versus control, outcome: 1.38 Mortality with separated new trial data.



Health-related quality of life

Two instruments were used to measure HRQL: The CRQ was used in five studies involving 259 participants (Behnke 2000; Carr 2009; Eaton 2009; Man 2004; Seymour 2010), and the SGRQ was used in eight studies involving 846 participants (Borges 2014; Deepak 2014; Greening 2014; Ko 2011; Ko 2016; Man 2004; Murphy 2005; Seymour 2010).

High-quality evidence indicates that pulmonary rehabilitation after an exacerbation improves health-related quality of life (Summary of findings for the main comparison). The eight studies that used

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the SGRQ reported a statistically significant effect on total score, which was above the MID of four points (mean difference (MD) -7.80, 95% CI -12.12 to -3.47; Figure 7). Statistically significant and important effects (greater than MID) were also observed for the impact and activities domains of the SGRQ and for the dyspnoea, fatigue and emotional function domains of the CRQ (Analysis 1.3). Effects were not statistically significant for SGRQ symptoms nor for CRQ mastery domains. Again, heterogeneity was evident in all of these analyses, but most studies showed positive effects of pulmonary rehabilitation, with some studies observing large effects and others smaller but statistically significant effects. Extensive rehabilitation programmes showed larger effects than less extensive rehabilitation programmes, but differences between subgroups of trials (extensive vs less extensive programmes) were not statistically significant for CRQ (Analysis 1.17) nor for SGRQ (Analysis 1.22). Subgroup analyses comparing trials with respect to length of follow-up were inconsistent. Although trials of short duration noted a smaller effect on the CRQ (Analysis 1.18), investigators reported a larger effect on the SGRQ (Analysis 1.23). Trials at high risk of bias with respect to concealment of random allocation showed statistically significantly larger effects on the SGRQ (Analysis 1.25), but other subgroup analyses revealed no statistically significant effects. Studies newly included in this update showed, on average, smaller effects of rehabilitation than were noted in earlier trials (Figure 8), but overall results did not change to an important extent compared with the earlier version of this review. One study involving 49 obese COPD participants (Torres-Sánchez 2015) used the EuroQol 5D instrument and found statistically significant effects of rehabilitation for the domains of self-care, usual activities, anxiety and depression, and for the visual analogue scale, but no effect for mobility and pain/discomfort domains.

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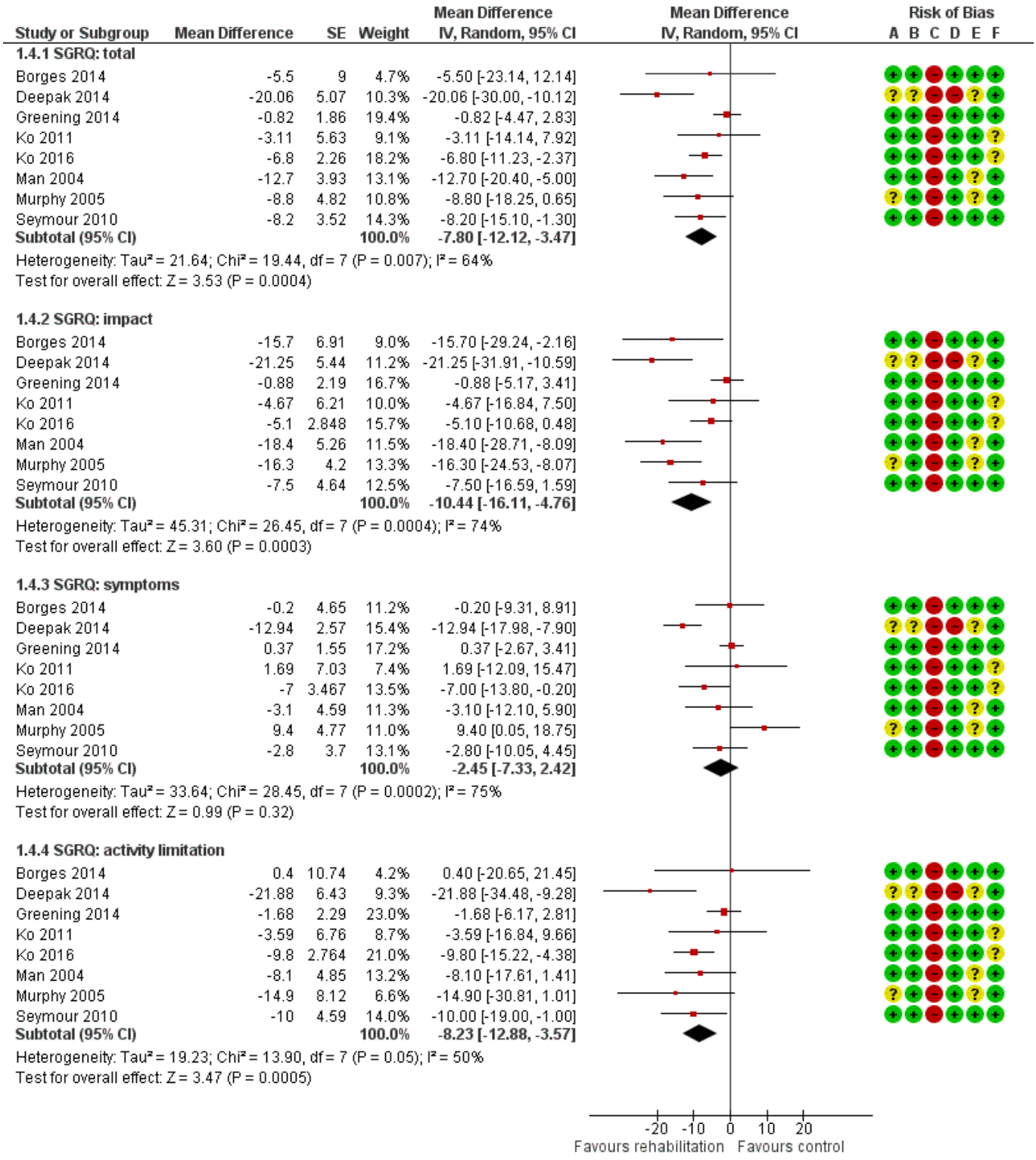
Figure 7. Forest plot of comparison: 1 Rehabilitation versus control, outcome: 1.4 Health-related quality of life: St George's Respiratory Questionnaire.



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding (performance bias and detection bias): Health-related quality of life
(**D**) Incomplete outcome data (attrition bias)
(**E**) Selective reporting (reporting bias)

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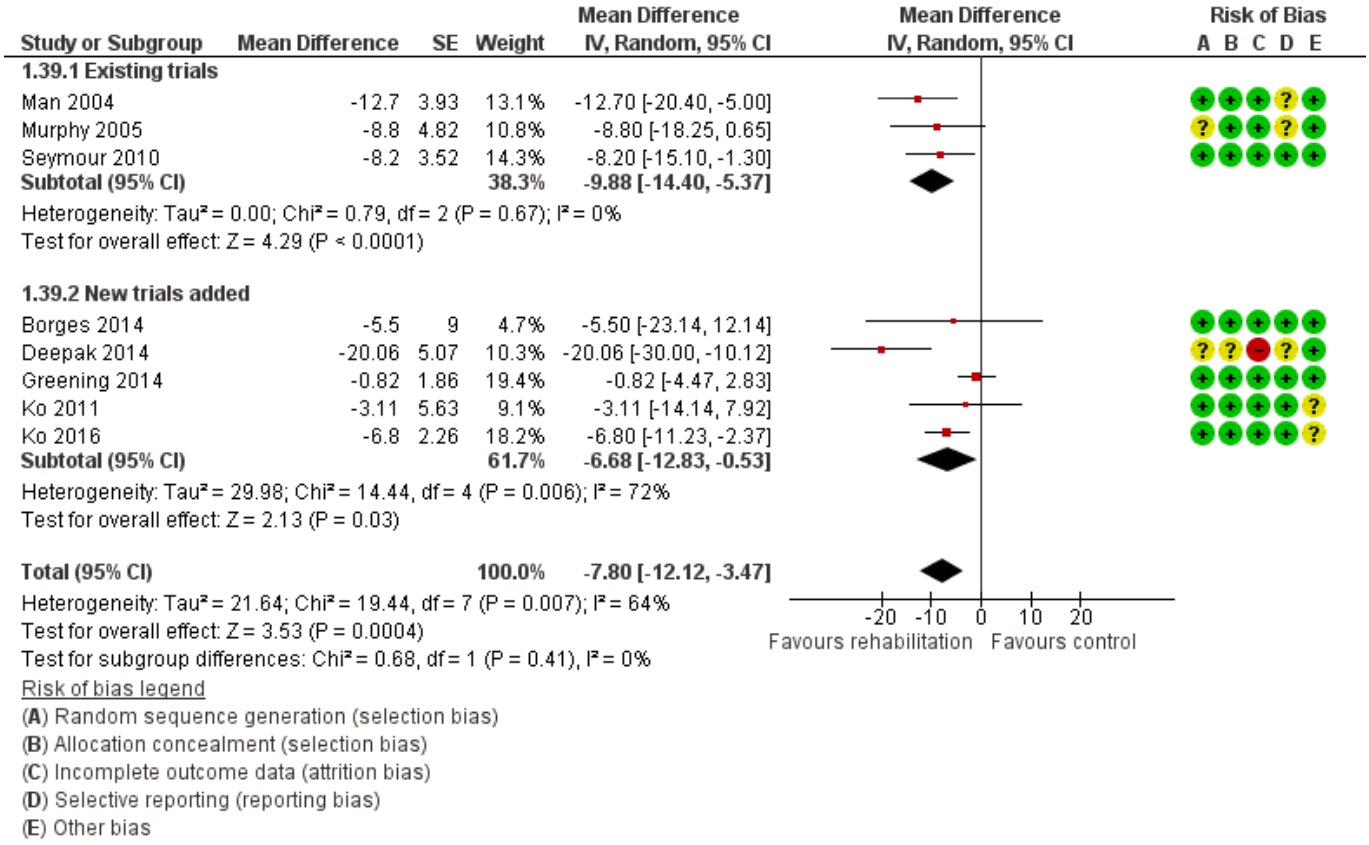
Figure 8. Forest plot of comparison: 1 Rehabilitation versus control, outcome: 1.39 Health-related quality of life: SGRQ total with separated new trial data.



Exercise capacity

Thirteen studies involving 819 participants used the six-minute walk test (Behnke 2000; Borges 2014; Carr 2009; Deepak 2014; Eaton 2009; He 2015; Kirsten 1998; Ko 2011; Ko 2016; Liao 2015; Nava 1998; Troosters 2002; Troosters 2010), and four studies involving 448 participants used the shuttle walk test to measure exercise capacity (Greening 2014; Man 2004; Murphy 2005; Seymour 2010). One study used the three-minute walk test (Tang 2012).

High-quality evidence (Summary of findings for the main comparison) shows that six-minute walk distance (6MWD) improved, on average, by 62 meters (95% CI 38 to 86; Figure 9) and shuttle walk test distance by 48 meters (95% CI -1 to 97; Analysis 1.6); these findings were not statistically significant. Again, much heterogeneity was evident, but most studies showed positive effects of pulmonary rehabilitation, and heterogeneity was driven particularly by differences between studies showing very large effects and studies showing smaller but statistically significant effects. Subgroup analysis comparing trials at low and high risk for bias with respect to concealment of random allocation (Analysis 1.30) showed statistically significantly smaller effects in trials at low risk of bias. Studies at high risk of bias, because they lacked blinding, showed statistically significantly larger effects on the shuttle walk test (Analysis 1.36), but no other subgroup analyses revealed a reason for heterogeneity (Analysis 1.27; Analysis 1.28; Analysis 1.29; Analysis 1.31 for 6MWD; Analysis 1.32; Analysis 1.33; Analysis 1.34; Analysis 1.35 for shuttle walk test). Three-minute walk distance increased more in the low-intensity exercise group than in the control group (effect size 0.4, 95% CI -0.5 to 1.3) or the high-intensity exercise group (effect size 0.6, 95% CI -0.3 to 1.5), but the differences were not statistically significant (Tang 2012). One study involving 49 obese patients with COPD (Torres-Sánchez 2015) used the EuroQol 5D instrument and found statistically significant effects of rehabilitation for the domains of self-care, usual activities, anxiety and depression and for the two-minute step-in-place test performed to assess exercise capacity, as well as a statistically significant effect of rehabilitation on the number of repetitions performed (increase of 17.6 vs 4.9 repetitions, with 47 repetitions reported at baseline (both groups)).

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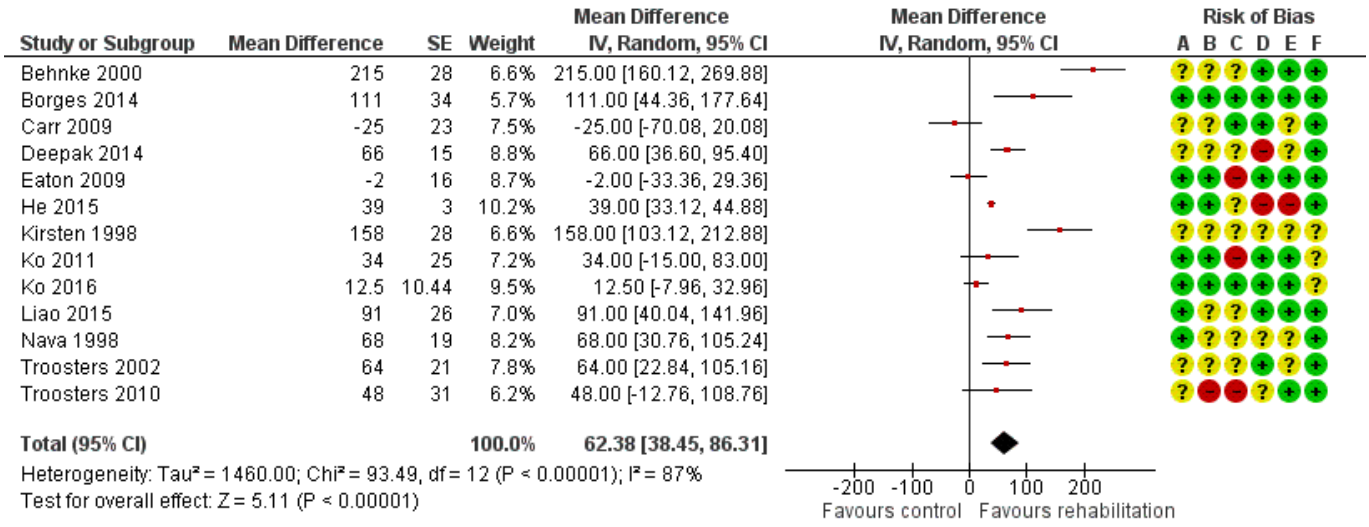
Figure 9. Forest plot of comparison: 1 Rehabilitation versus control, outcome: 1.5 Change from baseline in 6-minute walking test.



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding (performance bias and detection bias): Walk test
(**D**) Incomplete outcome data (attrition bias)
(**E**) Selective reporting (reporting bias)
(**F**) Other bias

Adverse events

Five studies involving 278 participants explicitly recorded adverse events (Behnke 2000; Eaton 2009; He 2015; Man 2004; Tang 2012). Four studies reported no adverse events during rehabilitation programmes. whereas one study (Tang 2012) reported one serious event that occurred when a participant felt unwell, but symptoms resolved within one hour and the participant continued with the rehabilitation programme.

DISCUSSION

Summary of main results

Overall evidence of high quality shows moderate to large effects of rehabilitation on health-related quality of life and exercise capacity in participants with chronic obstructive pulmonary disease (COPD) that are well above the minimal important difference (MID) for the Chronic Respiratory Questionnaire (CRQ), St George's Respiratory Questionnaire (SGRQ), the six-minute walk distance test (6MWD) and the shuttle walk distance test (Holland 2014; Jones 2005; Schunemann 2003; Schunemann 2005; Singh 2014). Some recent studies showed no significant effect of rehabilitation on hospital readmissions and mortality. and introduced heterogeneity as compared with the last update of this review. Such heterogeneity of effects on hospital readmissions and mortality is not fully understood at this point, which explains why review authors assigned only moderate quality to evidence showing statistically significant effects of rehabilitation on hospital readmissions, and low quality to evidence revealing its not statistically significant effect on mortality.

Overall completeness and applicability of evidence

The update of this systematic review was substantial in that review authors included 11 additional studies, and this more than doubled the number of included study participants. Updated meta-analyses that include a diverse set of trials informed the recent debate about how pulmonary rehabilitation has to be delivered to be beneficial for patients after acute exacerbations of COPD (Maddocks 2015). This debate began because more recent trials (Carr 2009; Eaton 2009; Greening 2014; Ko 2011) showed smaller or no effects of pulmonary rehabilitation after acute exacerbations of COPD compared with earlier versions of this systematic review (Puhan 2011). As we argued earlier (Puhan 2011), small trials tend to overestimate the effect of an intervention compared with large trials (Cappelleri 1996; Ioannidis 1998; Kjaergard 2001; LeLorier 1997). This phenomenon may be attributed in part to a publication bias, that is, the fact that small trials are more likely to be published if they show statistically significant treatment effects (Egger 1998). On the other hand, methodological shortcomings of small trials such as inadequate generation of the randomisation code, insufficient concealment of random allocation and lack of blinding may contribute to discrepancies between the results of single large trials and pooled estimates based on small trials (Kjaergard 2001). In our systematic review, included trials had methodological limitations, and some subgroup analyses revealed that risk of bias explains some of the heterogeneity noted for different outcomes. Hence, it cannot be excluded that estimates provided by the meta-analyses may represent overestimations of the effect of pulmonary rehabilitation after an acute exacerbation.

Indeed, the largest trial, which included 320 participants, showed no benefit of pulmonary rehabilitation for people with COPD as per

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separate data provided on this population (Greening 2014). However, this trial has been criticized for not offering an extensive pulmonary rehabilitation programme (Hopkinson 2014; Spruit 2014). Participants in the intervention group followed, on average, 2.6 supervised sessions during hospital admission, then received largely unsupervised training after discharge. Some may argue that we should not have included this trial in this systematic review because the intervention was not designed or implemented as a rehabilitation programme that is extensive enough to have an effect on hospital readmissions, mortality and other outcomes. It is difficult to draw a line to show when a programme qualifies as a pulmonary rehabilitation programme in accordance with international standards (ERS ATS Statement 2013), so we decided to use rather inclusive trial eligibility criteria. Such an approach offers the opportunity to explore reasons for heterogeneity across trials, which may be highly informative for practice. For this purpose, we applied a scoring approach to assess the extensiveness of a pulmonary rehabilitation programme (using addition and subtraction of points in a way that is similar to the GRADE approach). When developing this approach, we recognised that multiple criteria should be used rather than a single criterion, such as the number of completed training sessions or the combination of endurance and strength exercise. A single criterion is not sufficient for evaluation of complex interventions such as pulmonary rehabilitation, wherein multiple components act synergistically and introduce the risk of mis-classifying studies. Therefore, we considered the number of exercise training sessions, the frequency of exercise training and type and supervision of training, as well as self-management education, in assessing how extensive pulmonary rehabilitation programmes were (Assessment of heterogeneity). As much as possible, we aligned the cut-offs for upgrading and downgrading the extensiveness of rehabilitation programmes with the recent European Respiratory Society (ERS)-American Thoracic Society (ATS) statement (ERS ATS Statement 2013) and British Thoracic Society (BTS) guidelines on pulmonary rehabilitation (BTS 2013). Although two independent review authors assessed programmes and sought consensus, we cannot exclude that others may classify some programmes differently. However, Table 1 presents all reasons for downgrading or upgrading of evidence for each study.

Results of this systematic review suggest that it may matter how pulmonary rehabilitation is delivered. The eight trials that offered and implemented an extensive programme showed mostly large and consistent effects on readmissions, health-related quality of life and exercise capacity while also suggesting an effect on mortality. Although the programmes of these eight trials differed (see Characteristics of included studies and Table 1), all offered many training sessions (Behnke 2000; Nava 1998; Troosters 2002) or programmes long in duration (Behnke 2000; Troosters 2002), or they added extensive self-management education to the exercise programme (Ko 2016; Man 2004; Seymour 2010). The results of less extensive programmes are also important because some reflect barriers for implementation and uptake of pulmonary rehabilitation after acute exacerbations of COPD. For example, today's hospital admission for a COPD exacerbation is often too short in duration to permit initiation of a programme. Also, patients who are admitted are often old and have multiple conditions, which may render the uptake of pulmonary rehabilitation difficult. The transition from the inpatient to the outpatient setting and the organisation required along the continuum of care are challenging, and patients may not continue with rehabilitation or may not start at all. In some countries, reimbursement schemes do not allow for extensive rehabilitation programmes. All of these challenges have been recently summarised and discussed (ERS ATS Statement 2013).

The applicability of current evidence also requires consideration that the group of patients willing or motivated by their healthcare professionals to participate in rehabilitation is probably quite a select one. This does not preclude that patients with COPD in general would benefit from rehabilitation after an exacerbation, but one should be cautious in judging the applicability of the results of this systematic review and should consider local circumstances and barriers. Conducting trials on pulmonary rehabilitation after an exacerbation is challenging. First, recruitment of participants is difficult because many may not wish to be randomly allocated to different types of post exacerbation management in a situation of poor health status (Benzo 2015). One trial on pulmonary rehabilitation after an exacerbation was stopped because only a few participants could be recruited (Van den Berg 2015). Recruitment was very slow in one trial comparing rehabilitation after exacerbation with rehabilitation in a stable pulmonary state (Puhan 2012), and another trial had to be stopped before the recruitment target was reached (Spaar 2009). Second, individuals willing to participate in a trial are likely to have a preference for pulmonary rehabilitation. If they are randomised to the control group or to rehabilitation after a period of time, they might ask for pulmonary rehabilitation at any time during follow-up. Given the clear benefits of this intervention for patients in a stable condition as confirmed in meta-analyses (McCarthy 2015), patients who experience an exacerbation can hardly be refused access to rehabilitative strategies. Whatever design investigators choose, a careful discussion of ethical and methodological issues is necessary before large trials are under way.

Quality of the evidence

The quality of the evidence was moderate for hospital readmissions, low for mortality and high for health-related quality of life and exercise capacity. The main reason for downgrading the quality of evidence for hospital readmissions and mortality is the heterogeneity of results, with some trials showing positive effects of rehabilitation, some no effects and one even revealing a negative impact of rehabilitation on mortality (Greening 2014). In addition, none of the trials included mortality as a primary outcome, and most reported durations of follow-up that were too short for an effect of pulmonary rehabilitation on mortality to be detected. Reasons for downgrading or upgrading the quality of evidence are given in Summary of findings for the main comparison.

Potential biases in the review process

Strengths of this systematic review include the extensive literature search, rigorous adherence to a predefined protocol and successful contact with authors of the included studies, all of whom provided additional information about their data.

We split the studies into subgroups before we reviewed the results, but we defined the extensiveness of rehabilitation programmes in a somewhat arbitrary way.

Agreements and disagreements with other studies or reviews

Compared with pulmonary rehabilitation in patients with COPD in stable condition, the effect size of rehabilitation on health-related quality of life is similar among patients who have recently had an exacerbation of COPD. Mean differences between rehabilitation

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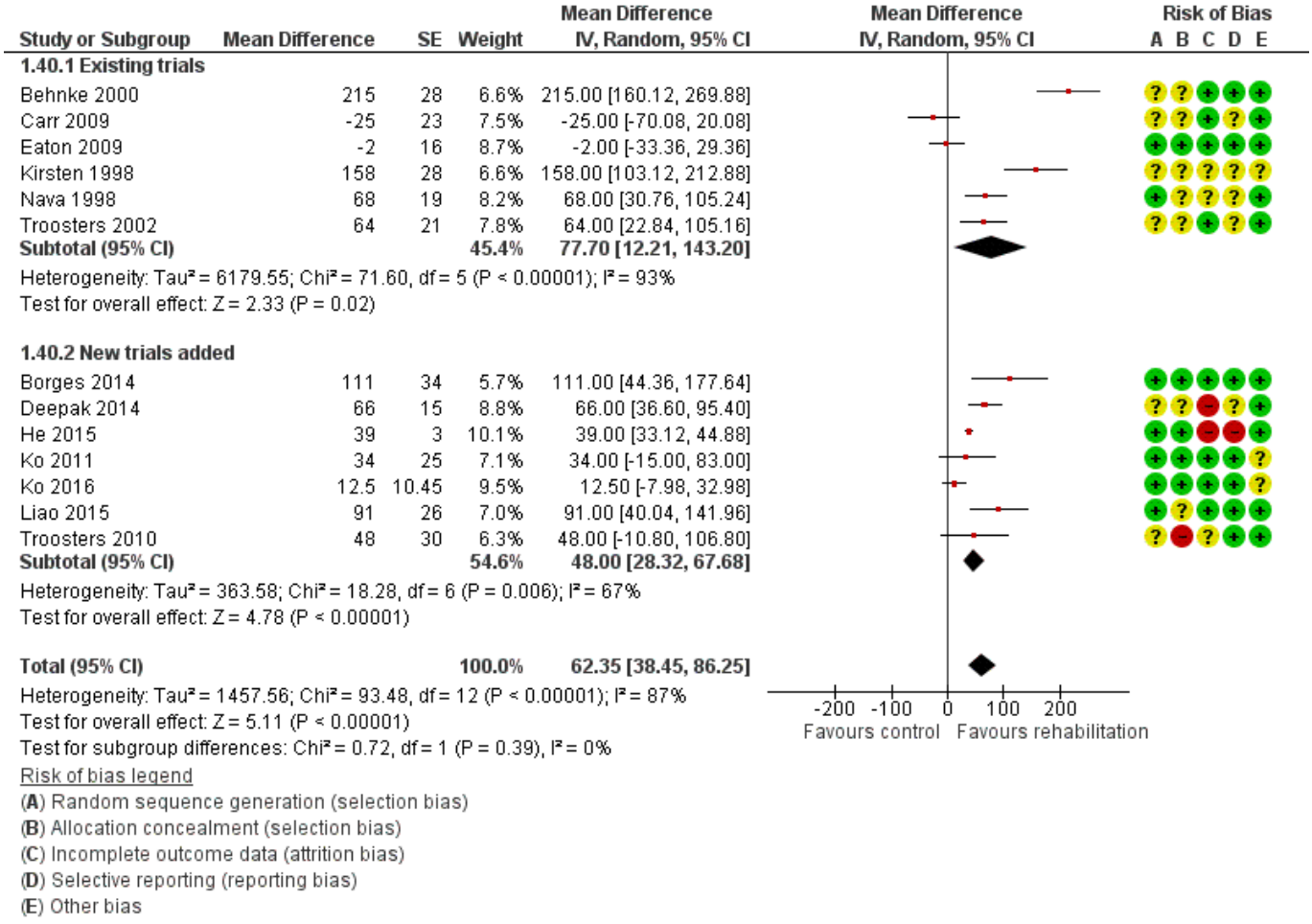
and control groups for CRQ dyspnoea, fatigue, emotional function and mastery domains in this Cochrane review were close to those observed in the Cochrane review on pulmonary rehabilitation for people with stable COPD (McCarthy 2015). Compared with the earlier version of this Cochrane review (Puhan 2011), the current evidence base is more diverse because different pulmonary rehabilitation programmes have been tested across a wide range of participants and settings around the world. Also, effect estimates became smaller with the addition of new trials (Figure 4; Figure 6; Figure 8; Figure 10)

Figure 10. Forest plot of comparison: 1 Rehabilitation versus control, outcome: 1.40 Change from baseline in 6-minute walking test with separated new trial data.



When only trials with an extensive rehabilitation programme were considered (Behnke 2000; He 2015; Ko 2011; Ko 2016; Man 2004; Nava 1998; Seymour 2010; Troosters 2002), the effects were larger than those seen in stable patients. Together with large improvements in exercise capacity and, in particular, substantial risk reduction for hospital admissions, pulmonary rehabilitation appears to be a particularly attractive addition to the treatment of patients after an exacerbation if an extensive rehabilitation programme can be implemented. Several possible explanations have been proposed for these large effects. First, as mentioned above, exacerbations lead to significant reductions in muscle function (Spruit 2003) and physical activity (Pitta 2006). This initial deterioration may render patients more likely to improve following pulmonary rehabilitation. Pulmonary rehabilitation is a particularly potent intervention for reverting physical inactivity (Troosters 2010a), and it has been shown that patients whose physical activity levels improve have less chance of being readmitted (Garcia-Aymerich 2006; Pitta 2006). Second, because eligible participants had been hospitalised for a COPD exacerbation, a deficiency in self-management or education may be evident among this group. This deficiency may be targeted in part by the rehabilitation intervention, and patient education may be of particular benefit for modifying behaviour in these patients. Indeed, a major study of a patient management programme that included home exercise for patients with COPD after an acute exacerbation reported impressive results (Bourbeau 2003). In this study, the mean number of hospital admissions per participant was reduced from 1.6 to 0.9 during the year following hospital admission for an acute exacerbation. It is well known from earlier studies that the recovery period is long, even for patients who have no further exacerbations, and that another exacerbation within six months can markedly limit recovery (Spencer 2003). A final explanation for the attractiveness of pulmonary rehabilitation programmes may be the effect of pulmonary rehabilitation on depressive symptoms after exacerbations. Depression is a significant risk factor for readmission, and pulmonary rehabilitation has been shown to improve depressive symptoms among

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depressed patients (Coventry 2007; Trappenburg 2005). Our meta-analyses show that pulmonary rehabilitation during the recovery period is superior to usual care in terms of prognosis and health-related quality of life.

Do we need more trials on pulmonary rehabilitation after COPD exacerbations?

A large body of available evidence from the systematic review on stable patients with COPD and from this systematic review shows large effects of pulmonary rehabilitation among patients with COPD (McCarthy 2015). Recently available trial findings show that many different exercise protocols are feasible and effective for patients with COPD, even if patients have poor health status, as is often the case during and after rehabilitation (ERS ATS Statement 2013). Exercise modalities include various forms of endurance and strength training, specific resistance training during hospital admission (Troosters 2010a), neuromuscular electrical stimulation and interval training, among others (ERS ATS Statement 2013; Sillen 2009).

Questions now may be focused less on the effectiveness of pulmonary rehabilitation after a COPD exacerbation in principle and more on how rehabilitation programmes should be designed and implemented, and how practitioners can foster patient uptake (ATS ERS Policy statement 2015). Uptake of pulmonary rehabilitation by patients is often low. In the Eaton trial, for example, 97 of 288 participants agreed to enrol in the trial; 47 were randomised to pulmonary rehabilitation, but only 19 of these 47 participants adhered to the rehabilitation programme (Eaton 2009). Those who adhered to the programme had substantially lower risk of readmission than participants who did not adhere to the rehabilitation programme, which corroborates the results of this Cochrane review showing that extensive rehabilitation programmes may be effective. Researchers should explore new ways of motivating patients to participate in pulmonary rehabilitation. For example, practitioners can explore the preferences of patients in terms of setting and type of exercise training, so the programme can be individualised according to both medical criteria and patient preferences. Also, the best timing for rehabilitation remains uncertain. Should rehabilitation start during an admission or shortly thereafter, or should it start when a patient's condition is stable again? An advantage of immediate rehabilitation after exacerbation is that it may provide a window of opportunity for patient education because patients may be more willing to change their health behaviour after an exacerbation. Also, continuity of care is possible if patients are immediately referred to pulmonary rehabilitation. A disadvantage of rehabilitation after exacerbation is that patients often re-exacerbate within weeks, so that the rehabilitation process is interrupted or even discontinued. Also, initiation of physical exercise is challenging for patients after an exacerbation, and more time may be needed to find the appropriate exercise protocol for an individual patient (Puhan 2005a). One trial addressed the comparison of early versus late rehabilitation after an exacerbation but failed to recruit enough participants (Puhan 2012).

The studies included in this Cochrane review had a median follow-up of three months. Given that physical exercise and self-management should be based on a long-term perspective, it is important for researchers to gather more data on health outcomes and costs over longer periods. Large and long-term randomised trials would be ideal for addressing these important questions, but they may not be feasible because of lack of funding, slow participant recruitment and other reasons, as explained above. Therefore, advanced observational study methods and analyses may be employed. Finally, more evidence on the cost-effectiveness of pulmonary rehabilitation in the post exacerbation setting is needed to inform policy decisions about pulmonary rehabilitation.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence of moderate quality (on average) from 20 studies (1477 participants) suggests that pulmonary rehabilitation is an effective intervention for post exacerbation treatment of patients with COPD. Effects leading to improved health-related quality of life and exercise capacity are large. Effects on hospital readmission were statistically significant in the meta-analysis but heterogenous across trials, and investigators need to explore whether the extensiveness of rehabilitation programmes explains such heterogeneity.

Implications for research

The decision to begin new trials of pulmonary rehabilitation should be made against the background of perceived ethics about the benefit of pulmonary rehabilitation after exacerbation and against the methodological and logistical challenges of such trials if comparisons include a no-exercise intervention. Studies should investigate how care providers can design and implement extensive rehabilitation programmes with a long-term perspective that are feasible, reimbursable and attractive enough for patients and healthcare providers. Trials should assess the best timing of pulmonary rehabilitation. Finally, formal cost-effectiveness analyses should be conducted to estimate the financial benefit derived from rehabilitation after COPD exacerbations.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Behnke 2000

Methods	Randomised parallel-group trial
Participants	26 participants with COPD (mean age 67 years, 77% males, mean FEV_1 36% predicted) after inpatient treatment for acute exacerbation
Interventions	**Rehabilitation:** within 4-7 days after admission, inpatient pulmonary rehabilitation with endurance exercise (5 walking sessions/d for 10 days), followed by 6 months of supervised home-based endurance exercise (3 walking sessions/d for 6 months). Completion rate of pulmonary rehabilitation: 65.2% (15/23 participants) **Usual care:** standard inpatient care without exercise and standard community care with respirologist. Follow-up: 76 weeks
Outcomes	CRQ, 6MWD, hospital readmission, mortality
Notes	Pulmonary rehabilitation programme was considered extensive (upgraded by +1 for > 30 exercise sessions and downgraded by -1 for unsupervised training). Financial support was provided by the Verein zur FoÈ rderung der Rehabilitationsforschung in Schleswig-Holstein e.V., Deutsche Gesellschaft fuer Medizinische Rehabilitation and Landesversicherungsanstalt Freie und Hansestadt, Hamburg, Germany.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available from trial report
Blinding (performance bias and detection bias) Hospital admission	Unclear risk	Information not available from trial report. Outcome may be affected by knowledge of treatment group assignment.

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Behnke 2000 *(Continued)*

Blinding (performance bias and detection bias) Health-related quality of life	High risk	Although unavoidable by definition, lack of blinding may affect outcome.
Blinding (performance bias and detection bias) Mortality	Low risk	Information not available from trial report. Outcome unlikely to be affected by knowledge of treatment group assignment
Blinding (performance bias and detection bias) Walk test	Unclear risk	Information not provided in trial report. Potential lack of blinding likely to affect outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up are detailed for both groups, and the final number of participants is balanced between comparison groups.
Selective reporting (reporting bias)	Low risk	Outcome reporting is sufficiently complete and transparent. Study authors provided individual participant data. Clinical trial registration number not reported
Other bias	Low risk	No indication of other biases

Borges 2014

Methods	Randomised parallel-group trial
Participants	29 participants with COPD (CG: n = 14, mean age 68 years, 71% males, mean FEV_1 39% predicted; IG: n = 15, mean age 64 years, 53% male, mean FEV_1 42% predicted) admitted to the hospital for treatment of COPD exacerbation
Interventions	**Rehabilitation:** exercise training started on third day of hospitalisation, inpatient pulmonary rehabilitation (completed 5.6 sessions on average) with whole-body resistance training for upper and lower limbs (session every morning with free weights in 2 sets of 8 repetitions). Completion rate of pulmonary rehabilitation: 95%. Follow-up: 1 month **Usual care:** Participants received normative daily care, including chest physiotherapy, non-invasive ventilation if needed and verbal instructions to carry on with their normative daily physical activities. Participants did not receive an exercise programme or a recommendation to exercise after hospital discharge. Follow-up: 1 month
Outcomes	SGRQ, 6MWD
Notes	Pulmonary rehabilitation programme was considered not extensive (downgraded by -2 for < 10 exercise training sessions and by -1 for strength training only). Financial support was provided by the Sao Paulo Research Foundation (Grant no. 2007/51-354-7) and the Brazilian Scientific Foundation (Grant no. 305987/2010-0). Clinical trial identifier: NCT01786928

Risk of bias

Bias	Authors' judgement	Support for judgement

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Borges 2014 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	"Allocation was concealed in sequentially numbered, sealed, opaque envelopes"
Blinding (performance bias and detection bias) Hospital admission	Unclear risk	Information not available from trial report
Blinding (performance bias and detection bias) Health-related quality of life	High risk	Information not available from trial report. Although unavoidable by definition, lack of blinding may affect outcome.
Blinding (performance bias and detection bias) Mortality	Unclear risk	Information not available from trial report
Blinding (performance bias and detection bias) Walk test	Low risk	"Evaluation[s] were performed by a blinded evaluator."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up are detailed for both groups, and the final number of participants is balanced between comparison groups.
Selective reporting (reporting bias)	Low risk	Outcome reporting is sufficiently complete and transparent. Clinical trial registration number is not reported.
Other bias	Low risk	No indication of other biases

Carr 2009

Methods	Randomised parallel-group trial
Participants	34 participants with COPD (mean age 68 years, 44% males, mean FEV_1 0.91 L) after inpatient treatment for acute exacerbation
Interventions	**Rehabilitation:** inpatient or outpatient pulmonary rehabilitation (based on participant preference or location of initial PR) (2 hours/session over 3 weeks, completed between 9 and 15 sessions) with breathing exercise, strength and interval training and corridor and treadmill walking or cycling; patient education (energy conservation, lung health, drugs and stress management). Completion rate of pulmonary rehabilitation: 94% (16/17 participants). Follow-up: 12 weeks **Usual care:** standard inpatient and community care without exercise (not further specified). Follow-up: 12 weeks
Outcomes	CRQ (primary outcome), 6MWD (secondary outcome)
Notes	Pulmonary rehabilitation programme was considered moderately extensive (downgraded by -1 for 10-15 exercise training sessions). Financial support provided by the Ontario Thoracic Society
Risk of bias	

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Carr 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; additional information not available from trial report
Allocation concealment (selection bias)	Unclear risk	Information not available from trial report
Blinding (performance bias and detection bias) Hospital admission	Unclear risk	Information not reported
Blinding (performance bias and detection bias) Health-related quality of life	High risk	Although unavoidable by definition, lack of blinding may affect outcome.
Blinding (performance bias and detection bias) Mortality	Low risk	Information not available from trial report. Outcome unlikely to be affected by knowledge of treatment group assignment
Blinding (performance bias and detection bias) Walk test	Low risk	"The investigator responsible for collecting outcome measures was unaware of group allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up are detailed for both groups, and the final number of participants is balanced between comparison groups.
Selective reporting (reporting bias)	Unclear risk	Outcome reporting is sufficiently complete and transparent: Results for all listed primary and secondary outcomes are reported. Clinical trial registration number not reported
Other bias	Low risk	No indication of other biases

Deepak 2014

Methods	Randomised parallel-group trial
Participants	60 participants with COPD (CG: mean age 58 years, 93% males, FEV_1 53% predicted; IG: mean age 59 years, 93% male, FEV_1 47% predicted) after admission for treatment of an acute exacerbation
Interventions	**Rehabilitation:** within 2 weeks after discharge, supervised outpatient pulmonary rehabilitation with limb strengthening and aerobic activities, education, nutrition and psychosocial rehabilitation for 12 weeks, including chest physiotherapy for drainage of secretions, breathing retraining techniques, techniques to control dyspnoea. Adherence to pulmonary rehabilitation not reported. Follow-up: 3 months **Usual care:** conventional treatment. Follow-up: 3 months
Outcomes	SGRQ, 6MWD
Notes	Extensiveness of pulmonary rehabilitation programme could not be assessed.
Risk of bias	

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Deepak 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described by study authors as follows: "randomisation was done by block randomisation technique"; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available from trial report
Blinding (performance bias and detection bias) Hospital admission	Unclear risk	Information not reported
Blinding (performance bias and detection bias) Health-related quality of life	High risk	Information not available from trial report. Although unavoidable by definition, lack of blinding may affect outcome.
Blinding (performance bias and detection bias) Mortality	Unclear risk	Information not reported
Blinding (performance bias and detection bias) Walk test	Unclear risk	Information not provided in trial report. Potential lack of blinding likely to affect outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal and drop-out rates are not reported.
Selective reporting (reporting bias)	Unclear risk	Outcome reporting is sufficiently complete and transparent: Results for all listed outcomes are reported. Clinical trial registration number not reported
Other bias	Low risk	No indication of other biases

Eaton 2009

Methods	Randomised parallel-group trial
Participants	97 participants with COPD (mean age 70 years, 44% males, mean FEV_1 36% predicted)
Interventions	**Rehabilitation:** The patient started inpatient programme as soon as medically appropriate, as determined by the attending medical team. Inpatient programme: supervised walking and upper/lower limb-strengthening exercise at least 30 minutes/d until discharge, followed by outpatient programme: supervised exercise for 8 weeks (1-hour session, twice weekly) and patient education (coping with dyspnoea, the importance of a regular daily home exercise programme, management of activities of daily living, drugs, vaccines, airway clearance techniques, nutritional advice, self-management and action plans for exacerbations, stress and panic management, relaxation techniques, mood disturbance, adapting to a chronic illness and end-of-life care). Only 19 (40%) patients assigned to early rehabilitation satisfied the a priori definition of adherence (attendance at 75% of rehabilitation sessions) Follow-up: 12 weeks **Usual care:** standardised care in accordance with ATS/ERS COPD guidelines and standardised advice on exercise and maintaining daily activities, but not further specified. Follow-up: 12 weeks
Outcomes	Hospital readmission and hospital days (primary outcomes); 6MWD, CRQ (secondary outcomes)

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Eaton 2009 *(Continued)*

Notes	Pulmonary rehabilitation programme was considered moderately extensive (downgraded by -2 for < 10 exercise training sessions but upgraded by +1 for extensive self-management training) Financial support provided by the Green Lane Research and Educational Foundation Clinical trial identifier: ACTRNO12605000372684

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Only information from computer available at time of randomisation
Blinding (performance bias and detection bias) Hospital admission	High risk	Outcome may be affected by knowledge of treatment group assignment.
Blinding (performance bias and detection bias) Health-related quality of life	High risk	Although unavoidable by definition, lack of blinding may affect outcome.
Blinding (performance bias and detection bias) Mortality	Low risk	Information not available from trial report. Outcome unlikely to be affected by knowledge of treatment group assignment
Blinding (performance bias and detection bias) Walk test	High risk	Lack of blinding likely to affect outcome assessment. "The nature of intervention precluded blinding of participants and health care providers."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up are detailed for both groups, and the final number of participants is balanced between comparison groups.
Selective reporting (reporting bias)	Low risk	Outcome reporting is sufficiently complete and transparent. Clinical trial registration number reported ACTRNO12605000372684
Other bias	Low risk	No indication of other biases

Greening 2014

Methods	Randomised parallel-group trial
Participants	389 participants (CG: n = 193, mean age 71 years, 44% males, mean FEV_1 57% predicted; IG: n = 196, mean age 71 years, 45% males, mean FEV_1 52% predicted) admitted to hospital for an exacerbation of chronic respiratory disease (320 (82%) patients with COPD; CG: n = 151; IG: n = 169)
Interventions	**Rehabilitation:** within 48 hours of hospital admission, supervised volitional (strength and aerobic training) and non-volitional (neuromuscular electrical stimulation) techniques (median duration of hospital admission 5 days). The mean number of sessions during the hospital admission was 2.7 (SD 2.6) for aerobic training, 2.5 (SD 1.9) for resistance training and 3.6 (SD 3.2) for neuromuscular electrical stimulation training. In addition, a self-management and educational package was offered. Completion

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Greening 2014 *(Continued)*

	rate of pulmonary rehabilitation: 86% for inpatient aerobic training, 90% for strength training and 90% for neuromuscular electrical stimulation training After discharge, participants received instructions on how to follow a progressive walking-based home exercise programme, to continue daily neuromuscular electrical stimulation and to follow the self-management programme. The postdischarge training was supported by telephone consultations from the pulmonary rehabilitation intervention team, using motivational interviewing techniques, at 48 hours, 2 weeks and 4 weeks. Continued daily adherence to the home programme was reported by 54% of participants for aerobic training and by 61% for resistance training. Follow-up: 12 months **Usual care:** standard care during hospital admission (median duration of hospital admission 5 days) including airway clearance techniques, mobility and advice on smoking cessation, dietetic advice and nutritional support if appropriate. No supervised or progressive exercise programme was provided during the admission or immediately after discharge, but outpatient pulmonary rehabilitation was offered to all participants 3 months after discharge. Follow-up: 12 months
Outcomes	Hospital readmissions, mortality (primary outcomes); SGRQ, ISWT and ESWT (secondary outcomes)
Notes	Pulmonary rehabilitation programme was considered moderately extensive (downgraded by -2 for mostly unsupervised training and upgraded by +1 for extensive self-management training). Financial support provided by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care in Leicestershire, Northamptonshire and Rutland (CLAHRC LNR), by the NIHR Leicester Respiratory Biomedical Research Unit and CLAHRC East Midlands, and by the University of Leicester Clinical Trials Unit Clinical trial identifier: ISRCTN05557928

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Automated Internet-based service (www.sealedenvelope.com)
Allocation concealment (selection bias)	Low risk	No details but can be assumed because of use of automated Internet-based service (www.sealedenvelope.com)
Blinding (performance bias and detection bias) Hospital admission	Unclear risk	Hospital admissions were captured through hospital databases and general practice records. Unclear if group assignment was known while hospital admissions were ascertained
Blinding (performance bias and detection bias) Health-related quality of life	High risk	Although unavoidable by definition, lack of blinding may affect outcome.
Blinding (performance bias and detection bias) Mortality	Low risk	Information not available from trial report. Outcome unlikely to be affected by knowledge of treatment group assignment
Blinding (performance bias and detection bias) Walk test	Low risk	"All investigators performing the outcome measures were blinded to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up are detailed for both groups, and the final number of participants is balanced between comparison groups. "We used an intention to treat analysis to assess the primary outcome."

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Greening 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	Information is reported in a sufficiently complete and transparent way. Clinical trial registration number reported
Other bias	Low risk	Supplemental details of methods and analysis reported

He 2015

Methods	Randomised parallel-group trial
Participants	94 participants (CG: n = 28, mean age 74 years, 82% males, mean FEV_1 39% predicted; IG: n = 66, mean age 69 years, 91% males, mean FEV_1 38% predicted) admitted to hospital for an exacerbation of chronic respiratory disease. 101 enrolled; 7 withdrew after randomisation (not included in analyses)
Interventions	**Rehabilitation:** from the second day of hospital admission, exercise training (endurance + strength, twice daily), relaxation and breathing retraining and education. The mean number of days of pulmonary rehabilitation was 9.1, which results in an average of 18 exercise sessions. Completion rate of pulmonary rehabilitation: not explicitly reported. Follow-up: in-hospital period (average, 9 days) **Usual care:** standard care during hospital admission (median duration of hospital admission, 10 days). Follow-up: in-hospital period (average, 10 days)
Outcomes	6MWD, CRQ, SGRQ, adverse events
Notes	Pulmonary rehabilitation programme was considered extensive. Financial support provided by grants from National Natural Science Foundation of China (81200044) and Shanghai Pujiang Program (12PJ1407800) and Research Fund for the Doctoral Program of Higher Education of China (20120072120070)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Information not available from trial report. Information requested of study authors: "method of random allocation by using a computer random number generator"
Allocation concealment (selection bias)	Low risk	Information not available from trial report. Information requested of study authors: "randomisation process was concealed from those responsible for recruiting patients using central telephone randomisation system"
Blinding (performance bias and detection bias) Hospital admission	Unclear risk	Information not reported
Blinding (performance bias and detection bias) Health-related quality of life	Unclear risk	Although unavoidable by definition, lack of blinding may affect outcome.
Blinding (performance bias and detection bias) Mortality	Unclear risk	Information not reported
Blinding (performance bias and detection bias)	Unclear risk	Information not available from trial report. Although unavoidable by definition, lack of blinding may affect outcome.

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He 2015 *(Continued)*
Walk test

Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up are not specified. Final number of participants is not balanced between comparison groups (intervention group, n = 66; control group. n = 28).
Selective reporting (reporting bias)	High risk	CRQ domain scores not reported. Clinical trial registration number not reported
Other bias	Low risk	No indication of other biases

Kirsten 1998

Methods	Randomised parallel-group trial
Participants	29 participants with COPD (mean age 64 years, 90% males, mean FEV_1 36% predicted) after inpatient treatment for acute exacerbation
Interventions	**Rehabilitation:** within 6 to 8 days after admission, inpatient pulmonary rehabilitation with endurance exercise (5 walking sessions/d for 10 days). Completion rate of pulmonary rehabilitation: not reported **Usual care:** standard inpatient care without exercise (not further specified). Follow-up: 11 days
Outcomes	6MWD
Notes	Pulmonary rehabilitation programme was considered moderately extensive (downgraded by -1 for partly unsupervised training) Financial support provided by the Landesversicherungsanstalt (LVA) Freie und Hansestadt Hamburg

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; additional information not available from trial report
Allocation concealment (selection bias)	Unclear risk	Information not available from trial report
Blinding (performance bias and detection bias) Hospital admission	Unclear risk	Information not reported
Blinding (performance bias and detection bias) Health-related quality of life	High risk	Information not available from trial report. Although unavoidable by definition, lack of blinding may affect outcome.
Blinding (performance bias and detection bias) Mortality	Low risk	Information not available from trial report. Outcome unlikely to be affected by knowledge of treatment group assignment
Blinding (performance bias and detection bias) Walk test	Unclear risk	Information not provided in trial report. Potential lack of blinding likely to affect outcome assessment

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Kirsten 1998 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up are not specified, although the final number of participants is balanced between comparison groups.
Selective reporting (reporting bias)	Unclear risk	Outcome reporting is sufficiently complete and transparent. Clinical trial registration number not reported
Other bias	Unclear risk	Unclear further potential bias

Ko 2011

Methods	Randomised parallel-group trial
Participants	60 participants with COPD (CG: n = 30, mean age 74 years, 1 female, mean FEV_1 41% predicted; IG: n = 30, mean age 73 years, 100% males, FEV_1 46% predicted) admitted with COPD exacerbation
Interventions	**Rehabilitation:** outpatient pulmonary rehabilitation (within 2-3 weeks after discharge) with endurance training for 8 weeks (3 sessions/wk, 2 hours each session), advice to perform home exercises for at least 20 minutes/d and education on breathing techniques and how to cope with daily activities. Completion rate of pulmonary rehabilitation: 73% (22/30). Follow-up: 12 months **Usual care:** instructions to have regular exercise. Follow-up: 12 months
Outcomes	SGRQ, 6MWD, hospital readmissions, emergency admissions, mortality
Notes	Pulmonary rehabilitation programme was considered extensive. Only a small proportion of participants received long-acting bronchodilators, which may have limited their ability to exercise. Financial support provided by the Hong Kong Lung Foundation Grant and the Respiratory Research Fund of the Chinese University of Hong Kong Clinical trial identifier: NCT00287625

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer programme (allocation by minimization) was used to assist the randomisation of subjects equally into each group taking into account five factors; age (< 70 or ≥ 70 years), gender, length of hospital admission (< 7 or ≥ 7 days), 6 min walk (6MW) test (< 100 or ≥ 100 m) and predicted FEV_1 (< 30 or ≥ 30%)."
Allocation concealment (selection bias)	Low risk	Used minimisation when allocation was concealed
Blinding (performance bias and detection bias) Hospital admission	Unclear risk	Information not available from trial report
Blinding (performance bias and detection bias) Health-related quality of life	High risk	Information not available from trial report. Although unavoidable by definition, lack of blinding may affect outcome.

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Ko 2011 *(Continued)*

Blinding (performance bias and detection bias) Mortality	Low risk	Information not available from trial report. Outcome unlikely to be affected by knowledge of treatment group assignment
Blinding (performance bias and detection bias) Walk test	High risk	Information not available from trial report. Although unavoidable by definition, lack of blinding may affect outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up are detailed for both groups, and the final number of participants is balanced between comparison groups. "We used intention-to-treat analyses for all subjects who had been randomised."
Selective reporting (reporting bias)	Low risk	Information is reported sufficiently complete and in a transparent way. Clinical trial number reported
Other bias	Unclear risk	Unclear further potential bias

Ko 2016

Methods	Randomised parallel-group trial
Participants	180 participants with COPD (mean age 75 years, 96% males, mean FEV_1 45% predicted) admitted for COPD exacerbation
Interventions	Rehabilitation: comprehensive programme with multi-disciplinary approach at discharge from hospital, which included respiratory nurse education, exercise training programme at home or a short course of outpatient pulmonary rehabilitation and management of COPD according to international guidelines. Participants were provided a telephone number of a healthcare provider for seeking advice. In addition, they received 3-monthly telephone calls. Completion rate of pulmonary rehabilitation sessions: 71%. Follow-up: 12 months Usual care: conventional medical treatment and follow-up as per normal practice. Follow-up: 12 months
Outcomes	Hospital readmission rate (primary outcome); SGRQ, 6MWD, mortality (secondary outcomes)
Notes	Pulmonary rehabilitation programme was considered extensive (downgraded by -1 for some unsupervised training and upgraded by +1 for comprehensive self-management programme). Clinical trial identifier: NCT01108835

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Minimisation was used that considered 5 potential confounders.
Allocation concealment (selection bias)	Low risk	By using minimisation, investigators ensured allocation concealment.
Blinding (performance bias and detection bias) Hospital admission	Unclear risk	Information about who collected the data not available from trial report

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Ko 2016 *(Continued)*

Blinding (performance bias and detection bias) Health-related quality of life	High risk	Although unavoidable by definition, lack of blinding may affect outcome.
Blinding (performance bias and detection bias) Mortality	Low risk	Information about who collected the data not available from trial report. Outcome unlikely to be affected by knowledge of treatment group assignment
Blinding (performance bias and detection bias) Walk test	Low risk	"the research assistant performing walking tests was neither involved in the delivery of the patient care nor aware of the randomization process/"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up are detailed for both groups, and the final number of participants is balanced between comparison groups. "Analyses were conducted according to intention-to-treat principle."
Selective reporting (reporting bias)	Low risk	Information is reported in a sufficiently complete and transparent way. Clinical trial number reported
Other bias	Unclear risk	Unclear further potential bias

Liao 2015

Methods	Randomised parallel-group trial
Participants	61 participants with COPD (mean age 70 years, 61% males, no FEV_1 data) admitted to hospital for a COPD exacerbation
Interventions	Rehabilitation: inpatient respiratory rehabilitation exercise training package consisting of walk training (2 sessions/d, 10 to 30 minutes per session), disease awareness, sputum clearance treatment, pursed lip breathing, upper limb exercise with deep breathing and nutrition management and health education. Follow-up: 4 days Usual care: health education. Follow-up: 4 days
Outcomes	6MWD
Notes	Pulmonary rehabilitation programme was considered moderately extensive (downgraded by -2 for < 10 exercise sessions; upgraded by +1 for comprehensive self-management training) Financial support provided by the Chest Hospital, Ministry of Health and Welfare, Taiwan (DOH100-HO-3053) Clinical trial identifier: NCT02329873

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Described as randomised via a coin toss
Allocation concealment (selection bias)	Unclear risk	Information not available from trial report

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Liao 2015 *(Continued)*

Blinding (performance bias and detection bias) Hospital admission	Unclear risk	Information not reported. Outcome not assessed
Blinding (performance bias and detection bias) Health-related quality of life	Unclear risk	Information not reported. Outcome not assessed
Blinding (performance bias and detection bias) Mortality	Unclear risk	Information not reported. Outcome not assessed
Blinding (performance bias and detection bias) Walk test	Unclear risk	Information not available from trial report. Although unavoidable by definition, lack of blinding may affect outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up are detailed for both groups, and the final number of participants is balanced between comparison groups.
Selective reporting (reporting bias)	Low risk	Information is reported in a sufficiently complete and transparent way. Clinical trial number reported
Other bias	Low risk	No indication of other biases

Man 2004

Methods	Randomised parallel-group trial
Participants	42 participants with COPD (mean age 70 years, 41% males, FEV_1 39% predicted) after inpatient treatment for acute exacerbation
Interventions	**Rehabilitation:** multi-disciplinary outpatient pulmonary rehabilitation (within 10 days of discharge) with endurance and strength exercise and patient education for 8 weeks (2 sessions/wk). Completion rate of pulmonary rehabilitation: 85.7% (18/21 participants) **Usual care:** standard community care with respirologist. Follow-up: 12 weeks
Outcomes	CRQ, SGRQ, ISWT, hospital readmission, hospital days, emergency admissions, mortality
Notes	Pulmonary rehabilitation programme was considered extensive (upgraded by +1 for extensive self-management training). Financial support provided by the British Lung Foundation Trevor Clay Memorial Grant. and by “Pursuing Perfection,” co-ordinated by the NHS Modernisation Agency

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A random number generator was our tool to assign an intervention to the first patient entering the study. We used the minimisation method to assign patients further to the intervention group, taking into account five factors: age (< 70 years or 70 years), sex, length of hospital admission (< 7 days or 7 days), in-

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Man 2004 *(Continued)*

		cremental shuttle walk distance at discharge (< 100 metres or 100 metres), and predicted forced expiratory volume in one second (FEV_1; < 30% or 30%)."
Allocation concealment (selection bias)	Low risk	Used minimisation when allocation was concealed
Blinding (performance bias and detection bias) Hospital admission	High risk	Lack of blinding may affect outcome assessment. "Owing to the nature of the intervention... it was not possible to blind the patients or the assessors (investigator responsible and members of the pulmonary rehabilitation team)."
Blinding (performance bias and detection bias) Health-related quality of life	High risk	Although unavoidable by definition, lack of blinding may affect outcome.
Blinding (performance bias and detection bias) Mortality	Low risk	Information not available from trial report. Outcome unlikely to be affected by knowledge of treatment group assignment.
Blinding (performance bias and detection bias) Walk test	High risk	Lack of blinding likely to affect outcome assessment. "Owing to the nature of the intervention... it was not possible to blind the patients or the assessors (investigator responsible and members of the pulmonary rehabilitation team)."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up are detailed for both groups, and the final number of participants is balanced between comparison groups. "We analysed data on intention to treat basis. We made no attempt to impute missing data from those participants who were lost to follow up."
Selective reporting (reporting bias)	Unclear risk	Information is reported in a sufficiently complete and transparent way. Clinical trial number not reported
Other bias	Low risk	No indication of other biases

Murphy 2005

Methods	Randomised parallel-group trial
Participants	26 participants with COPD (mean age 66 years, 65% males, mean FEV_1 40% predicted) after home-for-hospital treatment for acute exacerbation
Interventions	**Rehabilitation:** supervised home-based pulmonary rehabilitation with endurance and strength exercise for 6 weeks (2 supervised sessions/wk and daily unsupervised sessions). Completion rate of pulmonary rehabilitation: 76.9% (10/13 participants) **Usual care:** standard community care with respirologist. Follow-up: 26 weeks
Outcomes	SGRQ, EQ-5D, ISWT, 3-minute step test, hospital readmission
Notes	Dr Murphy provided standard deviations for SGRQ measurements. Pulmonary rehabilitation programme was considered moderately extensive (downgraded by -1 for 10 to 15 exercise training sessions). Financial support not reported

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Murphy 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised" - Although the process of generating the randomisation schedule was not specified, it was presumed done because of efforts made with allocation concealment.
Allocation concealment (selection bias)	Low risk	"...each patient was randomly assigned in a 1:1 ratio for the home exercise group or a control group (standard care group) using blinded sealed envelopes."
Blinding (performance bias and detection bias) Hospital admission	Unclear risk	Information not reported
Blinding (performance bias and detection bias) Health-related quality of life	High risk	Although unavoidable by definition, lack of blinding may affect outcome.
Blinding (performance bias and detection bias) Mortality	Low risk	Information not available from trial report. Outcome unlikely to be affected by knowledge of treatment group assignment
Blinding (performance bias and detection bias) Walk test	Unclear risk	Information not provided in trial report. Potential lack of blinding likely to affect outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up are detailed for both groups, and the final number of participants is balanced between comparison groups.
Selective reporting (reporting bias)	Unclear risk	Information is reported in a sufficiently complete and transparent way. Clinical trial number not reported
Other bias	Low risk	No indication of other biases

Nava 1998

Methods	Randomised parallel-group trial
Participants	70 participants with COPD (mean age 66 years, 73% males, mean FEV_1 32% predicted, 76% needed mechanical ventilation) admitted to inpatient care for treatment of acute exacerbation
Interventions	**Rehabilitation**: within 3 to 5 days after admission, inpatient pulmonary rehabilitation with 4 steps of increasing intensity Step I, if unable to walk: mobilisation and strength training for lower extremities Step II, if able to walk: endurance exercise (walking) Step III, if possible: endurance exercise (cycling and stair climbing) and respiratory muscle training Step IV, if possible: endurance exercise (cycling at highest tolerated intensity, 2 sessions/d for 3 weeks) Completion rate of pulmonary rehabilitation: 85.4% (41/48 participants)

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Nava 1998 *(Continued)*

	Usual care: only steps I and II. Follow-up: 6 weeks
Outcomes	6MWD, mortality
Notes	Pulmonary rehabilitation programme was considered extensive (upgraded by +1 for > 30 exercise sessions). Financial support not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described as randomised via a computer programme; additional information not available from trial report
Allocation concealment (selection bias)	Unclear risk	Information not available from trial report
Blinding (performance bias and detection bias) Hospital admission	Unclear risk	Information not available from trial report
Blinding (performance bias and detection bias) Health-related quality of life	High risk	Information not available from trial report. Although unavoidable by definition, lack of blinding may affect outcome.
Blinding (performance bias and detection bias) Mortality	Low risk	Information not available from trial report. Outcome unlikely to be affected by knowledge of treatment group assignment
Blinding (performance bias and detection bias) Walk test	Unclear risk	Information not provided in trial report. Potential lack of blinding likely to affect outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up are not specified. The final number of participants is balanced between groups according to 3:1 randomisation (intervention group n = 60 and control group n = 20).
Selective reporting (reporting bias)	Unclear risk	Outcome reporting is sufficiently complete and transparent. Clinical trial registration number not reported
Other bias	Low risk	No indication of other biases

Seymour 2010

Methods	Randomised parallel-group trial
Participants	60 participants with COPD (mean age 66 years, 82% males, mean FEV_1 52% predicted) after inpatient treatment of acute exacerbation
Interventions	**Rehabilitation**: within a week after hospital discharge, outpatient pulmonary rehabilitation twice-weekly exercise (limb strengthening and aerobic activities) and education sessions, during 8 weeks. Completion rate of pulmonary rehabilitation: 77% (23/30). Participants were provided general informa-

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Seymour 2010 *(Continued)*

	tion about COPD and were offered outpatient appointments with general practitioner or respiratory team. Follow-up: 12 weeks **Usual care**: Participants were provided general information about COPD and were offered outpatient appointments with general practitioner or respiratory team. Not referred further Follow-up: 12 weeks
Outcomes	Exacerbation with hospitalisation (primary outcome), ISWT, ESWT, CRQ and SGRQ (secondary)
Notes	Pulmonary rehabilitation programme was considered extensive (downgraded by -1 for 10 to 15 exercise training sessions, and upgraded by +1 for extensive self-management training). Financial support provided by the British Lung Foundation Clinical trial identifier: NCT00557115

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were allocated by concealed randomisation by a statistician. The minimisation method matched groups for age (< 70 years or ≥ 70 years), sex (male or female), predicted FEV_1 (< 30% or ≥ 30%), duration of admission (< 7 or ≥ 7 days) and baseline ISWT (< 100 m or ≥ 100 m)."
Allocation concealment (selection bias)	Low risk	Used minimisation when allocation was concealed
Blinding (performance bias and detection bias) Hospital admission	High risk	Authors state: "Due to the nature of the intervention, it was not possible to blind subjects to their allocation."
Blinding (performance bias and detection bias) Health-related quality of life	High risk	"Due to the nature of the intervention, it was not possible to blind subjects to their allocation." Although unavoidable by definition, lack of blinding may affect outcome.
Blinding (performance bias and detection bias) Mortality	Low risk	Information not available from trial report. Outcome unlikely to be affected by knowledge of treatment group assignment
Blinding (performance bias and detection bias) Walk test	High risk	Authors state: "Due to the nature of the intervention, it was not possible to blind subjects to their allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up are well specified, and the final number of participants is balanced between comparison groups. "Participants were analysed on an intention-to-treat basis regardless of compliance."
Selective reporting (reporting bias)	Low risk	Outcome reporting is sufficiently complete and transparent: Results for all listed primary and secondary outcomes were reported. Clinical trial registration number reported
Other bias	Low risk	No indication of other biases

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Tang 2012

Methods	Randomised parallel-group trial
Participants	32 participants with COPD (CG: mean age 78 years, 55% males, mean FEV_1 47% predicted; low-Intensity IG: mean age 68 years, 45% males, mean FEV_1 45% predicted; high-Intensity IG: mean age 74 years, 20% males, mean FEV_1 46% predicted) after inpatient treatment of acute exacerbation
Interventions	**Rehabilitation**: Within 2 days after admission, inpatient exercise programme followed twice-daily 15-minute exercise sessions, in addition to standard physical therapy treatment. Low-intensity group walked at 40% and high-intensity group at 70% of the 3-minute walk test for 7.5 minutes; upper and lower limb resistance exercise was also done. Adherence to pulmonary rehabilitation was 78% in the low-intensity group and 71% in the high-intensity group. Follow-up: until hospital discharge **Usual care**: once-daily physical therapy (sputum clearance techniques, mobility and functional training)
Outcomes	Adverse events (primary outcome), 3MWD (secondary outcome)
Notes	Pulmonary rehabilitation programme was considered slightly extensive (downgraded by -2 for < 10 exercise training sessions). Financial support not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"A block randomisation allocation sequence was generated using a web-based program."
Allocation concealment (selection bias)	Unclear risk	"Principal investigator unsealed envelopes sequentially and allocated patients after baseline assessment."
Blinding (performance bias and detection bias) Hospital admission	Unclear risk	Information not reported
Blinding (performance bias and detection bias) Health-related quality of life	Unclear risk	Infromation not reported
Blinding (performance bias and detection bias) Mortality	Unclear risk	Information not available from trial report. Outcome unlikely to be affected by knowledge of treatment group assignment
Blinding (performance bias and detection bias) Walk test	Unclear risk	"RCT blinded to baseline and discharge assessments"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up are specified, and the final number of participants is balanced between comparison groups.
Selective reporting (reporting bias)	Low risk	Outcome reporting is sufficiently complete and transparent: Results for all listed primary and secondary outcomes were reported. Clinical trial registration number not reported
Other bias	Low risk	No indication of other biases

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Torres-Sánchez 2014

Methods	Randomised parallel-group trial
Participants	60 participants with COPD (mean age 71 years, 93% males, FEV_1 not reported) admitted for treatment of non-infectious exacerbation
Interventions	**Rehabilitation**: daily resistance lower limbs and controlled breathing exercises for 45 minutes. No other information reported **Usual care**: standard medical treatment
Outcomes	SGRQ
Notes	Information extracted from conference meeting abstract. Study authors have not published the data. Extensiveness of pulmonary rehabilitation programme could not be assessed. Financial support not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"were randomly allocated to a control or an intervention group"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Hospital admission	Unclear risk	Not reported
Blinding (performance bias and detection bias) Health-related quality of life	Unclear risk	Not reported
Blinding (performance bias and detection bias) Mortality	Unclear risk	Not reported
Blinding (performance bias and detection bias) Walk test	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Not reported

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Torres-Sánchez 2015

Methods	Randomised parallel-group trial
Participants	49 participants with COPD and body mass index (BMI) ≥ 30 kg/cm^2 and admitted to the hospital for ≥ 7 days for a COPD exacerbation (CG: mean age 74 years, 91% males, mean FEV_1 41% predicted, mean BMI 34 kg/cm^2; IG: mean age 72 years, 100% males, mean FEV_1 39% predicted, mean BMI 34 kg/cm^2
Interventions	**Rehabilitation**: twice-daily individualised and supervised multi-modal PR during 30 to 45 minutes. Programme included deep breathing, range of motion and upper and lower limb muscle strengthening exercises and 20 to 30 minutes of limb exercises. Adherence to PR not reported, but participants needed ≥ 7 training sessions to be considered for the analyses. It is unclear how many participants were excluded because they completed fewer than 7 sessions. **Usual care**: standard medical therapy, including systemic steroids, inhaled bronchodilators and oxygen
Outcomes	2-Minute step-in-place test, EuroQol (EQ-5D)
Notes	Pulmonary rehabilitation programme was considered moderately extensive (downgraded by -1 for 10 to 15 exercise training sessions). Financial support provided by the professional association of physiotherapists of Andalusia, Spain (Colegio Profesional de Fisioterapeutas de Andalucía) and the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) and the Spanish Foundation of the Lung (Fundación Respira)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	An independent nurse assigned participants to IG or CG according to a computer-generated randomisation list. The nurse informed the physiotherapist once participants had given their approval to participate in the study.
Blinding (performance bias and detection bias) Hospital admission	Unclear risk	NA
Blinding (performance bias and detection bias) Health-related quality of life	High risk	Although unavoidable by definition, lack of blinding may affect outcome.
Blinding (performance bias and detection bias) Mortality	Unclear risk	NA
Blinding (performance bias and detection bias) Walk test	Unclear risk	Unclear who supervised the 2-minute step-in-place test
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Adherence to PR not reported, but participants needed ≥ 7 training sessions to be considered for the analyses. It is unclear how many participants were excluded because they completed fewer than 7 sessions.
Selective reporting (reporting bias)	Unclear risk	Unclear if some measures taken at baseline (e.g. SGRQ) were not used as outcomes

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Torres-Sánchez 2015 *(Continued)*

Other bias	Unclear risk	No indication of other biases

Troosters 2002

Methods	Randomised parallel-group trial
Participants	43 participants with COPD (mean age 62 years, 85% males, FEV_1 39% predicted) after inpatient treatment for acute exacerbation
Interventions	**Rehabilitation:** outpatient pulmonary rehabilitation with endurance and strength exercise for 6 months (3 sessions/wk in first 3 months, then 2 sessions/wk). Completion rate of pulmonary rehabilitation: 70.8% (17/24 participants) **Usual care:** standard community care with respirologist (not further specified). Follow-up: 208 weeks
Outcomes	6MWD, mortality
Notes	Pulmonary rehabilitation programme was considered extensive (upgraded by +1 for > 30 exercise sessions). Financial support provided by the Fonds voor Wetenschappelijk Onderzoek-Vlaanderen (G0189.97 and G0175.99), Levenslijn Grant 7.0002.94, and Onderzoeksfonds, KU Leuven, Grant 27/98

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; additional information not available from trial report
Allocation concealment (selection bias)	Unclear risk	Information not available from trial report
Blinding (performance bias and detection bias) Hospital admission	Unclear risk	Information not available from trial report. Outcome unlikely to be affected by knowledge of treatment group assignment
Blinding (performance bias and detection bias) Health-related quality of life	High risk	Information not provided in trial report. Although unavoidable by definition, lack of blinding may affect outcome.
Blinding (performance bias and detection bias) Mortality	Low risk	Information not available from trial report. Outcome unlikely to be affected by knowledge of treatment group assignment
Blinding (performance bias and detection bias) Walk test	Unclear risk	Information not provided in trial report. Potential lack of blinding likely to affect outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up are specified, and the final number of participants is balanced between comparison groups.
Selective reporting (reporting bias)	Unclear risk	Outcome reporting is sufficiently complete and transparent. Clinical trial registration number not reported

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Troosters 2002 *(Continued)*

Other bias	Low risk	No indication of other biases

Troosters 2010

Methods	Randomised parallel-group trial
Participants	36 participants with COPD (CG: n = 19, mean age 69 years, 74% males, FEV_1 50% predicted; IG: n = 17, mean age 67 years, 76% males, FEV_1 40% predicted) admitted for treatment for acute exacerbation
Interventions	**Rehabilitation:** daily quadriceps resistance training for 7 days. Follow-up: 8 days **Usual care:** medical usual care plus mucous secretion clearance techniques and breathing exercises. Follow-up: 8 days
Outcomes	6MWD
Notes	Pulmonary rehabilitation programme was considered not extensive (downgraded by -2 for < 10 exercise training sessions, and by -1 when only strength training was offered). Financial support provided by the Research Foundation, Flanders grants KAN 1.5.139.06N and G.0386.05N Clinical trial identifier: NCT00877084

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised via "opaque envelopes prepared by an independent secretary"
Allocation concealment (selection bias)	High risk	"Tests were performed by researchers who were not blind to the allocation of the patients."
Blinding (performance bias and detection bias) Hospital admission	Unclear risk	Information not reported
Blinding (performance bias and detection bias) Health-related quality of life	Unclear risk	Information not reported
Blinding (performance bias and detection bias) Mortality	Unclear risk	Information not reported
Blinding (performance bias and detection bias) Walk test	High risk	Researchers and participants were not blind to the allocation group.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up are not specified, although the final number of participants is balanced between comparison groups.

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Troosters 2010 *(Continued)*

Selective reporting (reporting bias)	Low risk	Outcome reporting is sufficiently complete and transparent. Clinical trial registration number reported
Other bias	Low risk	Supplemental material on methods and analysis reported. No indication of other biases

3MWD: three-minute walking distance; 6MWD: six-minute walking distance; ATS: American Thoracic Society; BMI: body mass index; BODE index: body mass index, airflow obstruction, dyspnoea and exercise capacity index; CG: control group; COPD: chronic obstructive pulmonary disease; CRQ: Chronic Respiratory Questionnaire; EQ-5D: EuroQoL questionnaire; ERS: European Respiratory Society; ESWT: endurance shuttle walk test; FEV_1: forced expiratory volume in one second; h: hour; IG: intervention group; ISWT: incremental shuttle walk test; SF-36: short-form health survey; SGRQ: St George's Respiratory Questionnaire.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ali 2014	Not a randomised trial
Aljassem 2012	Not a randomised trial
Babu 2010	No control group without exercise training
Benzo 2015	Did not study intervention but provided reasons for non-participation in a trial
Puhan 2012	No control group without rehabilitation
Rasekaba 2009	Not a randomised trial
Saey 2011	Comment on Troosters 2010 trial
Tang 2013	Qualitative results from Tang 2012 trial
Torres-Sánchez 2013	Not a randomised trial
Zheng 2012	Not a randomised trial

Characteristics of ongoing studies *[ordered by study ID]*

Beekman 2014

Trial name or title	Reducing Exacerbations in Patients With Chronic Obstructive Pulmonary Disease With Physiotherapy
Methods	
Participants	
Interventions	
Outcomes	
Starting date	

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Beekman 2014 *(Continued)*

Contact information	
Notes	Study ongoing

Castelain 2008

Trial name or title	Early Rehabilitation of COPD Patients in ICU
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	Study has been terminated. No data published

Hughes 2015

Trial name or title	Pulmonary Rehabilitation and ACTIvity after COPD Exacerbations: the PRACTICE trial
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	Recruiting participants

Knaut 2014

Trial name or title	Evaluation of Aerobic Exercise Program During Hospitalization in Quality of Life and in Exercise Capacity After One Month of Discharge in Exacerbated COPD
Methods	
Participants	

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Knaut 2014 *(Continued)*

Interventions	
Outcomes	
Starting date	
Contact information	
Notes	Abstracts/22nd Annual Congress, Munich, Germany, 6-10 September 2014

Morante 2013

Trial name or title	Impact of Early Respiratory Rehabilitation in the Exacerbations of Re-admitted COPD Patients
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	Recruiting participants

Spielmanns 2015

Trial name or title	Effect of Pneumological Rehabilitation After an Acute Exacerbation of COPD (Chronic Obstructive Pulmonary Disease)
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	Not recruiting

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Stickland 2015

Trial name or title	Examining Pulmonary Rehabilitation on Discharged COPD Patients
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	Recruiting participants

DATA AND ANALYSES

Comparison 1. Rehabilitation versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital readmission (to end of follow-up)	8	810	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.21, 0.91]
2 Mortality	6	670	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.28, 1.67]
3 Health-related quality of life: Chronic Respiratory Disease Questionnaire (CRQ)	5		Mean Difference (Random, 95% CI)	Subtotals only
3.1 CRQ: dyspnoea domain	5		Mean Difference (Random, 95% CI)	0.97 [0.35, 1.58]
3.2 CRQ: fatigue domain	5		Mean Difference (Random, 95% CI)	0.81 [0.16, 1.45]
3.3 CRQ: emotional function domain	5		Mean Difference (Random, 95% CI)	0.94 [0.46, 1.42]
3.4 CRQ: mastery domain	5		Mean Difference (Random, 95% CI)	0.93 [-0.13, 1.99]
4 Health-related quality of life: St George's Respiratory Questionnaire	8		Mean Difference (Random, 95% CI)	Subtotals only
4.1 SGRQ: total	8		Mean Difference (Random, 95% CI)	-7.80 [-12.12, -3.47]
4.2 SGRQ: impact	8		Mean Difference (Random, 95% CI)	-10.44 [-16.11, -4.76]
4.3 SGRQ: symptoms	8		Mean Difference (Random, 95% CI)	-2.45 [-7.33, 2.42]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4 SGRQ: activity limitation	8		Mean Difference (Random, 95% CI)	-8.23 [-12.88, -3.57]
5 Change from baseline in 6-minute walking test	13		Mean Difference (Random, 95% CI)	62.38 [38.45, 86.31]
6 Change from baseline in shuttle walk test	4		Mean Difference (Random, 95% CI)	48.14 [-1.03, 97.32]
7 Subgroup analysis hospital readmission: extensiveness of rehabilitation programme	8	810	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.21, 0.91]
7.1 Extensive rehab programmes	5	367	Odds Ratio (M-H, Random, 95% CI)	0.28 [0.10, 0.78]
7.2 Less-extensive rehab programmes	3	443	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.44, 1.93]
8 Subgroup analysis hospital readmission: length of follow-up	8	587	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.22, 0.76]
8.1 Follow-up >3 months	5	389	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.24, 1.06]
8.2 Follow-up ≤3 months	3	198	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.06, 0.98]
9 Subgroup analysis hospital readmission: generation of random sequence	8	810	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.21, 0.91]
9.1 Low risk of bias	6	758	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.25, 1.19]
9.2 Unclear or high risk of bias	2	52	Odds Ratio (M-H, Random, 95% CI)	0.16 [0.04, 0.59]
10 Subgroup analysis hospital readmission: concealment of random allocation	8	810	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.21, 0.91]
10.1 Low risk of bias	7	784	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.25, 1.08]
10.2 Unclear or high risk of bias	1	26	Odds Ratio (M-H, Random, 95% CI)	0.09 [0.01, 0.56]
11 Subgroup analysis hospital readmission: blinding	8	810	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.21, 0.91]
11.1 Low risk of bias	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Unclear or high risk of bias	8	810	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.21, 0.91]
12 Subgroup analysis mortality: extensiveness of rehabilitation programme	6	670	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.28, 1.67]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Extensive rehab programmes	5	350	Odds Ratio (M-H, Random, 95% CI)	0.50 [0.26, 0.99]
12.2 Less-extensive rehab programmes	1	320	Odds Ratio (M-H, Random, 95% CI)	1.88 [1.06, 3.33]
13 Subgroup analysis mortality: length of follow-up	6	670	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.28, 1.67]
13.1 Follow-up >3 months	5	629	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.26, 1.86]
13.2 Follow-up ≤3 months	1	41	Odds Ratio (M-H, Random, 95% CI)	0.5 [0.04, 5.99]
14 Subgroup analysis mortality: generation of random sequence	6	670	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.28, 1.67]
14.1 Low risk of bias	4	601	Odds Ratio (M-H, Random, 95% CI)	1.10 [0.52, 2.34]
14.2 Unclear or high risk of bias	2	69	Odds Ratio (M-H, Random, 95% CI)	0.25 [0.08, 0.83]
15 Subgroup analysis mortality: concealment of random allocation	6	670	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.28, 1.67]
15.1 Low risk of bias	4	601	Odds Ratio (M-H, Random, 95% CI)	1.10 [0.52, 2.34]
15.2 Unclear or high risk of bias	2	69	Odds Ratio (M-H, Random, 95% CI)	0.25 [0.08, 0.83]
16 Subgroup analysis mortality: blinding	6	670	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.28, 1.67]
16.1 Low risk of bias	6	670	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.28, 1.67]
16.2 Unclear or high risk of bias	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17 Subgroup analysis CRQ dyspnoea domain: extensiveness of rehabilitation programme	5		Mean Difference (Random, 95% CI)	Subtotals only
17.1 Extensive rehab programmes	3		Mean Difference (Random, 95% CI)	1.31 [0.63, 2.00]
17.2 Less-extensive rehab programmes	2		Mean Difference (Random, 95% CI)	0.37 [-0.50, 1.24]
18 Subgroup analysis CRQ dyspnoea domain: length of follow-up	5		Mean Difference (Random, 95% CI)	0.97 [0.35, 1.58]
18.1 Follow-up >3 months	1		Mean Difference (Random, 95% CI)	2.44 [1.42, 3.46]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.2 Follow-up ≤3 months	4		Mean Difference (Random, 95% CI)	0.70 [0.12, 1.28]
19 Subgroup analysis CRQ dyspnoea domain: generation of random sequence	5		Mean Difference (Random, 95% CI)	0.97 [0.35, 1.58]
19.1 Low risk of bias	3		Mean Difference (Random, 95% CI)	0.65 [-0.07, 1.37]
19.2 Unclear or high risk of bias	2		Mean Difference (Random, 95% CI)	1.65 [0.14, 3.16]
20 Subgroup analysis CRQ dyspnoea domain: concealment of random allocation	5		Mean Difference (Random, 95% CI)	0.97 [0.35, 1.58]
20.1 Low risk of bias	3		Mean Difference (Random, 95% CI)	0.65 [-0.07, 1.37]
20.2 Unclear or high risk of bias	2		Mean Difference (Random, 95% CI)	1.65 [0.14, 3.16]
21 Subgroup analysis CRQ dyspnoea domain: blinding	5		Mean Difference (Random, 95% CI)	0.97 [0.35, 1.58]
21.1 Low risk of bias	0		Mean Difference (Random, 95% CI)	0.0 [0.0, 0.0]
21.2 Unclear or high risk of bias	5		Mean Difference (Random, 95% CI)	0.97 [0.35, 1.58]
22 Subgroup analysis SGRQ total score: extensiveness of rehabilitation programme	8		Mean Difference (Random, 95% CI)	Subtotals only
22.1 Extensive rehab programmes	4		Mean Difference (Random, 95% CI)	-7.82 [-11.03, -4.61]
22.2 Less-extensive rehab programmes	4		Mean Difference (Random, 95% CI)	-8.49 [-18.13, 1.15]
23 Subgroup analysis SGRQ total score: length of follow-up	8		Mean Difference (Random, 95% CI)	-7.80 [-12.12, -3.47]
23.1 Follow-up >3 months	4		Mean Difference (Random, 95% CI)	-4.27 [-8.32, -0.22]
23.2 Follow-up ≤3 months	4		Mean Difference (Random, 95% CI)	-12.09 [-17.61, -6.57]
24 Subgroup analysis SGRQ total score: generation of random sequence	8		Mean Difference (Random, 95% CI)	-7.80 [-12.12, -3.47]
24.1 Low risk of bias	6		Mean Difference (Random, 95% CI)	-5.87 [-9.87, -1.88]
24.2 Unclear or high risk of bias	2		Mean Difference (Random, 95% CI)	-14.32 [-25.35, -3.29]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25 Subgroup analysis SGRQ total score: concealment of random allocation	8		Mean Difference (Random, 95% CI)	-7.80 [-12.12, -3.47]
25.1 Low risk of bias	7		Mean Difference (Random, 95% CI)	-6.12 [-9.73, -2.51]
25.2 Unclear or high risk of bias	1		Mean Difference (Random, 95% CI)	-20.06 [-28.00, -10.12]
26 Subgroup analysis SGRQ total score: blinding	8		Mean Difference (Random, 95% CI)	-7.80 [-12.12, -3.47]
26.1 Low risk of bias	0		Mean Difference (Random, 95% CI)	0.0 [0.0, 0.0]
26.2 Unclear or high risk of bias	8		Mean Difference (Random, 95% CI)	-7.80 [-12.12, -3.47]
27 Subgroup analysis 6-minute walking test: extensiveness of rehabilitation programme	13		Mean Difference (Random, 95% CI)	59.70 [35.09, 84.31]
27.1 Extensive rehab programmes	6		Mean Difference (Random, 95% CI)	65.50 [31.71, 99.30]
27.2 Less-extensive rehab programmes	7		Mean Difference (Random, 95% CI)	54.91 [6.07, 103.74]
28 Subgroup analysis 6-minute walk test: length of follow-up	13		Mean Difference (Random, 95% CI)	59.70 [35.09, 84.31]
28.1 Follow-up >3 months	4		Mean Difference (Random, 95% CI)	78.95 [1.95, 155.96]
28.2 Follow-up ≤3 months	9		Mean Difference (Random, 95% CI)	52.21 [24.72, 79.70]
29 Subgroup analysis 6-minute walk test: generation of random sequence	13		Mean Difference (Random, 95% CI)	59.70 [35.09, 84.31]
29.1 Low risk of bias	7		Mean Difference (Random, 95% CI)	34.89 [14.17, 55.61]
29.2 Unclear or high risk of bias	6		Mean Difference (Random, 95% CI)	86.44 [25.63, 147.24]
30 Subgroup analysis 6-minute walk test: concealment of random allocation	13		Mean Difference (Random, 95% CI)	62.38 [38.44, 86.32]
30.1 Low risk of bias	5		Mean Difference (Random, 95% CI)	29.55 [6.15, 52.95]
30.2 Unclear or high risk of bias	8		Mean Difference (Random, 95% CI)	84.16 [40.23, 128.09]
31 Subgroup analysis 6-minute walk test: blinding	13		Mean Difference (Random, 95% CI)	62.38 [38.44, 86.32]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.1 Low risk of bias	3		Mean Difference (Random, 95% CI)	26.31 [-30.62, 83.25]
31.2 Unclear or high risk of bias	10		Mean Difference (Random, 95% CI)	74.02 [44.81, 103.23]
32 Subgroup analysis shuttle walk test: extensiveness of rehabilitation programme	4		Mean Difference (Random, 95% CI)	48.11 [-0.74, 96.95]
32.1 Extensive rehab programmes	2		Mean Difference (Random, 95% CI)	58.45 [35.02, 81.88]
32.2 Less-extensive rehab programmes	2		Mean Difference (Random, 95% CI)	37.68 [-69.92, 145.28]
33 Subgroup analysis shuttle walk test: length of follow-up	4		Mean Difference (Random, 95% CI)	48.14 [-1.03, 97.32]
33.1 Follow-up >3 months	2		Mean Difference (Random, 95% CI)	37.68 [-69.92, 145.28]
33.2 Follow-up ≤3 months	2		Mean Difference (Random, 95% CI)	58.77 [34.85, 82.69]
34 Subgroup analysis shuttle walk test: generation of random sequence	4		Mean Difference (Random, 95% CI)	48.14 [-1.03, 97.32]
34.1 Low risk of bias	3		Mean Difference (Random, 95% CI)	35.41 [-18.04, 88.86]
34.2 Unclear or high risk of bias	1		Mean Difference (Random, 95% CI)	96.0 [37.20, 154.80]
35 Subgroup analysis shuttle walk test: concealment of random allocation	4		Mean Difference (Random, 95% CI)	48.14 [-1.03, 97.32]
35.1 Low risk of bias	4		Mean Difference (Random, 95% CI)	48.14 [-1.03, 97.32]
35.2 Unclear or high risk of bias	0		Mean Difference (Random, 95% CI)	0.0 [0.0, 0.0]
36 Subgroup analysis shuttle walk test: blinding	4		Mean Difference (Random, 95% CI)	48.14 [-1.03, 97.32]
36.1 Low risk of bias	1		Mean Difference (Random, 95% CI)	-14.0 [-39.48, 11.48]
36.2 Unclear or high risk of bias	3		Mean Difference (Random, 95% CI)	64.58 [41.49, 87.66]
37 Hospital readmission (to end of follow-up) with separated new trial data	8	810	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.21, 0.91]
37.1 Existing trials	5	250	Odds Ratio (M-H, Random, 95% CI)	0.22 [0.08, 0.58]

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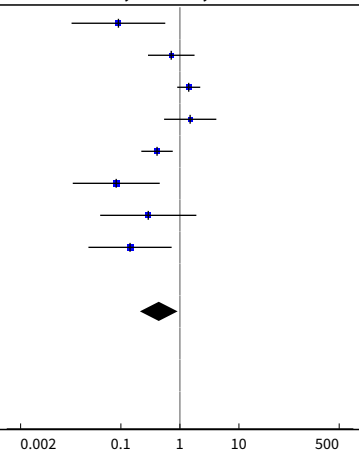
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
37.2 New trials added	3	560	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.38, 2.26]
38 Mortality with separated new trial data	6	670	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.28, 1.67]
38.1 Existing trials	3	110	Odds Ratio (M-H, Random, 95% CI)	0.28 [0.10, 0.84]
38.2 New trials added	3	560	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.48, 2.71]
39 Health-related quality of life: SGRQ total with separated new trial data	8		Mean Difference (Random, 95% CI)	-7.80 [-12.12, -3.47]
39.1 Existing trials	3		Mean Difference (Random, 95% CI)	-9.88 [-14.40, -5.37]
39.2 New trials added	5		Mean Difference (Random, 95% CI)	-6.68 [-12.83, -0.53]
40 Change from baseline in 6 minute walking test with separated new trial data	13		Mean Difference (Random, 95% CI)	62.35 [38.45, 86.25]
40.1 Existing trials	6		Mean Difference (Random, 95% CI)	77.70 [12.21, 143.20]
40.2 New trials added	7		Mean Difference (Random, 95% CI)	48.00 [28.32, 67.68]

Analysis 1.1. Comparison 1 Rehabilitation versus control, Outcome 1 Hospital readmission (to end of follow-up).

Study or subgroup	Pulmonary rehab n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Behnke 2000	3/14	9/12		8.77%	0.09[0.01,0.56]
Eaton 2009	11/47	15/50		14.78%	0.71[0.29,1.77]
Greening 2014	108/169	84/151		17.79%	1.41[0.9,2.21]
Ko 2011	16/30	13/30		13.96%	1.49[0.54,4.14]
Ko 2016	44/90	63/90		16.84%	0.41[0.22,0.76]
Man 2004	2/20	12/21		9.46%	0.08[0.02,0.45]
Murphy 2005	2/13	5/13		8.52%	0.29[0.04,1.9]
Seymour 2010	2/30	10/30		9.89%	0.14[0.03,0.72]
Total (95% CI)	**413**	**397**		**100%**	**0.44[0.21,0.91]**
Total events: 188 (Pulmonary rehab), 211 (Control)					
Heterogeneity: Tau^2=0.74; Chi^2=29.8, df=7(P=0); I^2=76.51%					
Test for overall effect: Z=2.2(P=0.03)					



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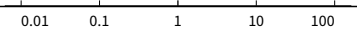
Analysis 1.2. Comparison 1 Rehabilitation versus control, Outcome 2 Mortality.

Study or subgroup	Pulmonary rehab n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Behnke 2000	1/14	1/12		7.53%	0.85[0.05,15.16]
Greening 2014	41/169	22/151		30.49%	1.88[1.06,3.33]
Ko 2011	0/30	2/30		6.79%	0.19[0.01,4.06]
Ko 2016	10/90	12/90		25.83%	0.81[0.33,1.99]
Man 2004	1/20	2/21		9.45%	0.5[0.04,5.99]
Troosters 2002	6/24	12/19		19.91%	0.19[0.05,0.72]
Total (95% CI)	**347**	**323**		**100%**	**0.68[0.28,1.67]**
Total events: 59 (Pulmonary rehab), 51 (Control)					
Heterogeneity: Tau^2=0.6; Chi^2=12.19, df=5(P=0.03); I^2=58.97%					
Test for overall effect: Z=0.83(P=0.41)					



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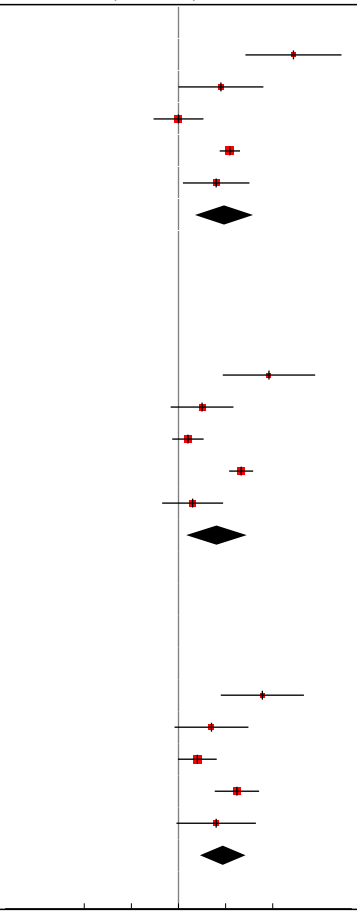
Analysis 1.3. Comparison 1 Rehabilitation versus control, Outcome 3 Health-related quality of life: Chronic Respiratory Disease Questionnaire (CRQ).

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.3.1 CRQ: dyspnoea domain						
Behnke 2000	0	0	2.4 (0.52)		15.39%	2.44[1.42,3.46]
Carr 2009	0	0	0.9 (0.46)		16.94%	0.9[-0,1.8]
Eaton 2009	0	0	0 (0.27)		22.22%	0[-0.53,0.53]
Man 2004	0	0	1.1 (0.11)		25.74%	1.09[0.87,1.31]
Seymour 2010	0	0	0.8 (0.36)		19.71%	0.8[0.09,1.51]
Subtotal (95% CI)					**100%**	**0.97[0.35,1.58]**
Heterogeneity: Tau^2=0.37; Chi^2=22.33, df=4(P=0); I^2=82.09%						
Test for overall effect: Z=3.07(P=0)						
1.3.2 CRQ: fatigue domain						
Behnke 2000	0	0	1.9 (0.5)		15.46%	1.92[0.94,2.9]
Carr 2009	0	0	0.5 (0.34)		19.17%	0.5[-0.17,1.17]
Eaton 2009	0	0	0.2 (0.17)		22.69%	0.2[-0.13,0.53]
Man 2004	0	0	1.3 (0.13)		23.28%	1.33[1.08,1.58]
Seymour 2010	0	0	0.3 (0.33)		19.4%	0.3[-0.35,0.95]
Subtotal (95% CI)					**100%**	**0.81[0.16,1.45]**
Heterogeneity: Tau^2=0.44; Chi^2=36.63, df=4(P<0.0001); I^2=89.08%						
Test for overall effect: Z=2.46(P=0.01)						
1.3.3 CRQ: emotional function domain						
Behnke 2000	0	0	1.8 (0.45)		15.53%	1.78[0.9,2.66]
Carr 2009	0	0	0.7 (0.4)		17.43%	0.7[-0.08,1.48]
Eaton 2009	0	0	0.4 (0.21)		26.1%	0.4[-0.01,0.81]
Man 2004	0	0	1.2 (0.24)		24.67%	1.24[0.77,1.71]
Seymour 2010	0	0	0.8 (0.43)		16.26%	0.8[-0.04,1.64]
Subtotal (95% CI)					**100%**	**0.94[0.46,1.42]**
Heterogeneity: Tau^2=0.19; Chi^2=11.66, df=4(P=0.02); I^2=65.69%						



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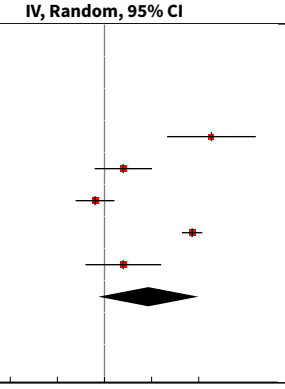
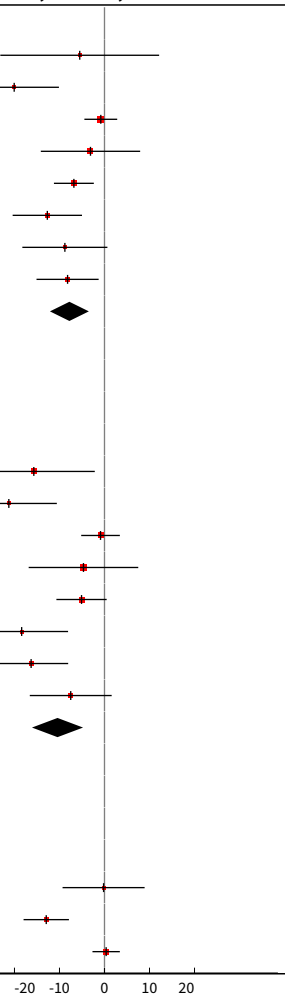
Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Test for overall effect: Z=3.81(P=0)						
1.3.4 CRQ: mastery domain						
Behnke 2000	0	0	2.3 (0.48)		18.43%	2.27[1.33,3.21]
Carr 2009	0	0	0.4 (0.31)		20.13%	0.4[-0.21,1.01]
Eaton 2009	0	0	-0.2 (0.21)		20.88%	-0.2[-0.61,0.21]
Man 2004	0	0	1.9 (0.11)		21.37%	1.86[1.64,2.08]
Seymour 2010	0	0	0.4 (0.41)		19.18%	0.4[-0.4,1.2]
Subtotal (95% CI)					**100%**	**0.93[-0.13,1.99]**
Heterogeneity: Tau²=1.36; Chi²=94.24, df=4(P<0.0001); I²=95.76%						
Test for overall effect: Z=1.72(P=0.09)						



Analysis 1.4. Comparison 1 Rehabilitation versus control, Outcome 4 Health-related quality of life: St George's Respiratory Questionnaire.

Study or subgroup	Rehabilitation N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.4.1 SGRQ: total						
Borges 2014	0	0	-5.5 (9)		4.74%	-5.5[-23.14,12.14]
Deepak 2014	0	0	-20.1 (5.07)		10.28%	-20.06[-30,-10.12]
Greening 2014	0	0	-0.8 (1.86)		19.39%	-0.82[-4.47,2.83]
Ko 2011	0	0	-3.1 (5.63)		9.12%	-3.11[-14.14,7.92]
Ko 2016	0	0	-6.8 (2.26)		18.19%	-6.8[-11.23,-2.37]
Man 2004	0	0	-12.7 (3.93)		13.12%	-12.7[-20.4,-5]
Murphy 2005	0	0	-8.8 (4.82)		10.85%	-8.8[-18.25,0.65]
Seymour 2010	0	0	-8.2 (3.52)		14.3%	-8.2[-15.1,-1.3]
Subtotal (95% CI)					**100%**	**-7.8[-12.12,-3.47]**
Heterogeneity: Tau²=21.64; Chi²=19.44, df=7(P=0.01); I²=63.99%						
Test for overall effect: Z=3.53(P=0)						
1.4.2 SGRQ: impact						
Borges 2014	0	0	-15.7 (6.91)		9.01%	-15.7[-29.24,-2.16]
Deepak 2014	0	0	-21.2 (5.44)		11.2%	-21.25[-31.91,-10.59]
Greening 2014	0	0	-0.9 (2.19)		16.74%	-0.88[-5.17,3.41]
Ko 2011	0	0	-4.7 (6.21)		10%	-4.67[-16.84,7.5]
Ko 2016	0	0	-5.1 (2.848)		15.7%	-5.1[-10.68,0.48]
Man 2004	0	0	-18.4 (5.26)		11.49%	-18.4[-28.71,-8.09]
Murphy 2005	0	0	-16.3 (4.2)		13.32%	-16.3[-24.53,-8.07]
Seymour 2010	0	0	-7.5 (4.64)		12.55%	-7.5[-16.59,1.59]
Subtotal (95% CI)					**100%**	**-10.44[-16.11,-4.76]**
Heterogeneity: Tau²=45.31; Chi²=26.45, df=7(P=0); I²=73.53%						
Test for overall effect: Z=3.6(P=0)						
1.4.3 SGRQ: symptoms						
Borges 2014	0	0	-0.2 (4.65)		11.19%	-0.2[-9.31,8.91]
Deepak 2014	0	0	-12.9 (2.57)		15.36%	-12.94[-17.98,-7.9]
Greening 2014	0	0	0.4 (1.55)		17.15%	0.37[-2.67,3.41]



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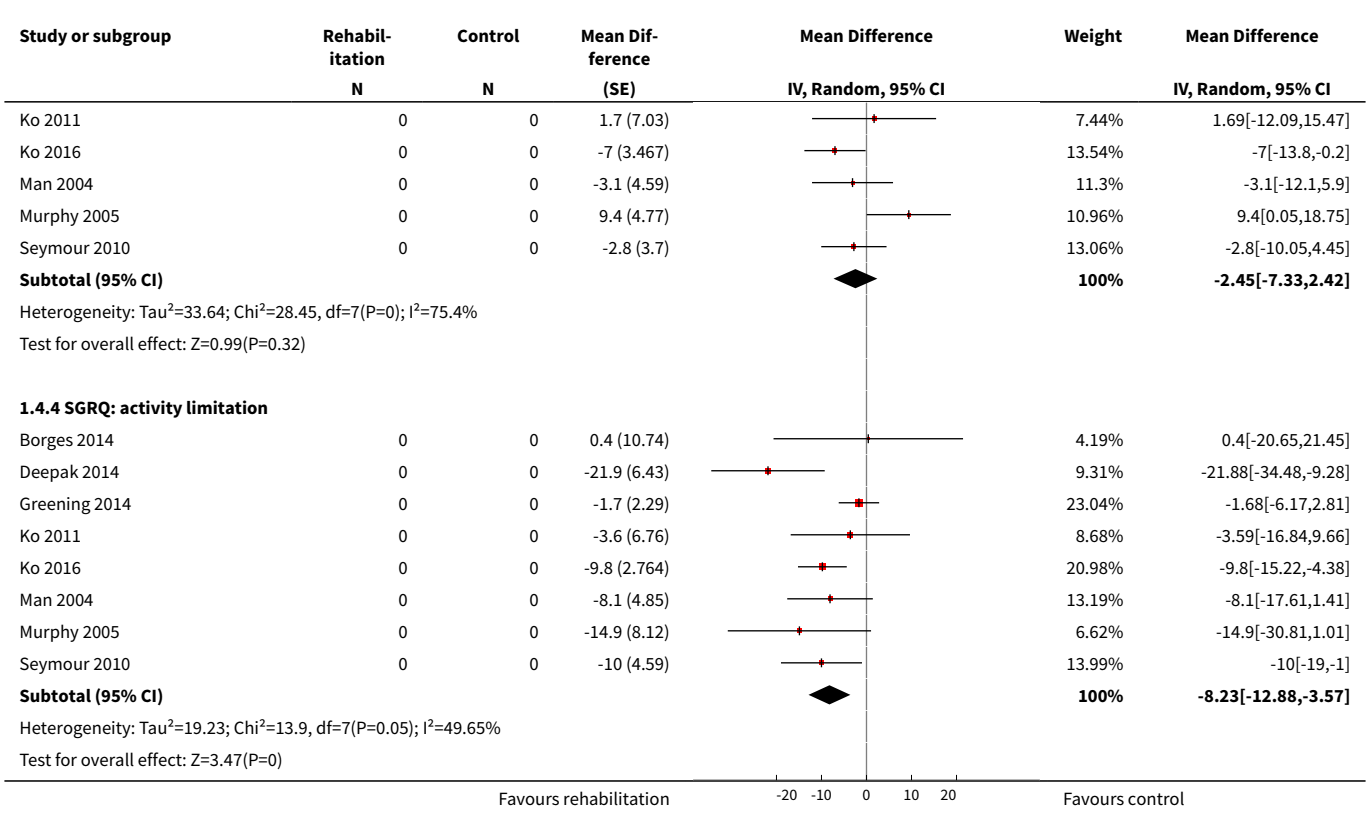
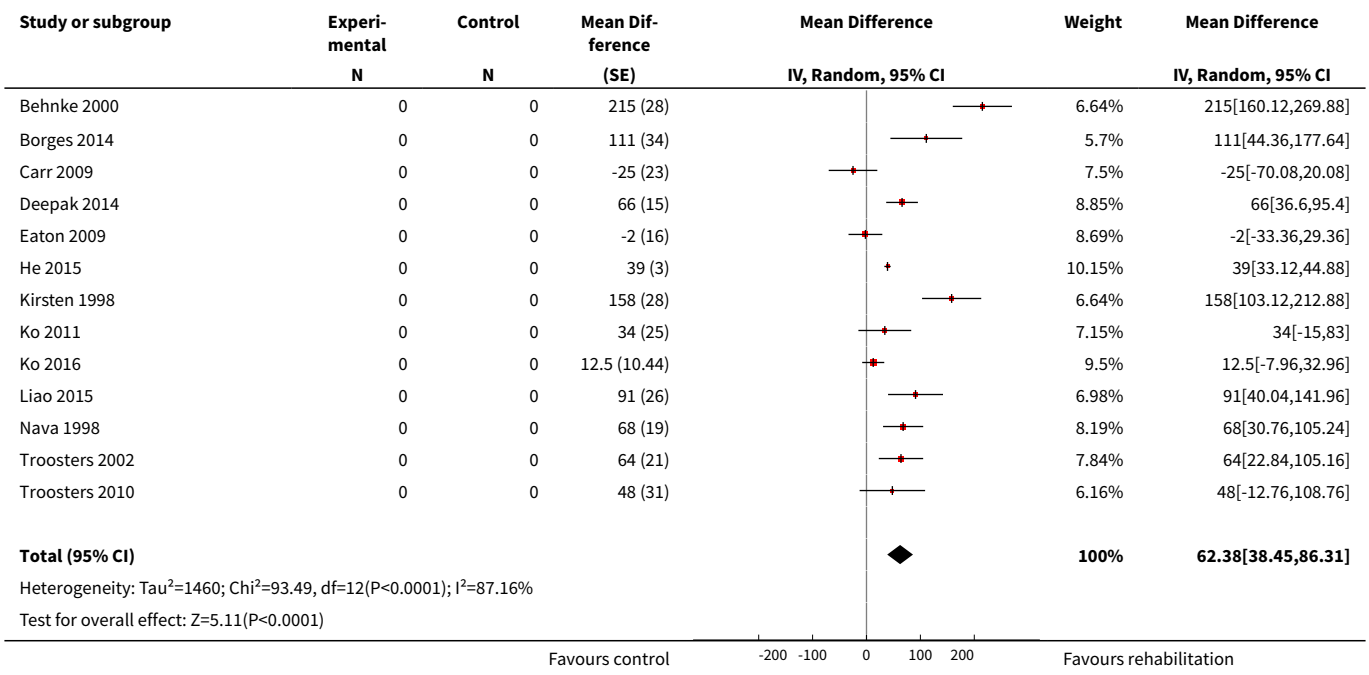


Study or subgroup	Rehabilitation N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Ko 2011	0	0	1.7 (7.03)		7.44%	1.69[-12.09,15.47]
Ko 2016	0	0	-7 (3.467)		13.54%	-7[-13.8,-0.2]
Man 2004	0	0	-3.1 (4.59)		11.3%	-3.1[-12.1,5.9]
Murphy 2005	0	0	9.4 (4.77)		10.96%	9.4[0.05,18.75]
Seymour 2010	0	0	-2.8 (3.7)		13.06%	-2.8[-10.05,4.45]
Subtotal (95% CI)					**100%**	**-2.45[-7.33,2.42]**
Heterogeneity: Tau²=33.64; Chi²=28.45, df=7(P=0); I²=75.4%						
Test for overall effect: Z=0.99(P=0.32)						
1.4.4 SGRQ: activity limitation						
Borges 2014	0	0	0.4 (10.74)		4.19%	0.4[-20.65,21.45]
Deepak 2014	0	0	-21.9 (6.43)		9.31%	-21.88[-34.48,-9.28]
Greening 2014	0	0	-1.7 (2.29)		23.04%	-1.68[-6.17,2.81]
Ko 2011	0	0	-3.6 (6.76)		8.68%	-3.59[-16.84,9.66]
Ko 2016	0	0	-9.8 (2.764)		20.98%	-9.8[-15.22,-4.38]
Man 2004	0	0	-8.1 (4.85)		13.19%	-8.1[-17.61,1.41]
Murphy 2005	0	0	-14.9 (8.12)		6.62%	-14.9[-30.81,1.01]
Seymour 2010	0	0	-10 (4.59)		13.99%	-10[-19,-1]
Subtotal (95% CI)					**100%**	**-8.23[-12.88,-3.57]**
Heterogeneity: Tau²=19.23; Chi²=13.9, df=7(P=0.05); I²=49.65%						
Test for overall effect: Z=3.47(P=0)						

Analysis 1.5. Comparison 1 Rehabilitation versus control, Outcome 5 Change from baseline in 6-minute walking test.



Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Behnke 2000	0	0	215 (28)		6.64%	215[160.12,269.88]
Borges 2014	0	0	111 (34)		5.7%	111[44.36,177.64]
Carr 2009	0	0	-25 (23)		7.5%	-25[-70.08,20.08]
Deepak 2014	0	0	66 (15)		8.85%	66[36.6,95.4]
Eaton 2009	0	0	-2 (16)		8.69%	-2[-33.36,29.36]
He 2015	0	0	39 (3)		10.15%	39[33.12,44.88]
Kirsten 1998	0	0	158 (28)		6.64%	158[103.12,212.88]
Ko 2011	0	0	34 (25)		7.15%	34[-15,83]
Ko 2016	0	0	12.5 (10.44)		9.5%	12.5[-7.96,32.96]
Liao 2015	0	0	91 (26)		6.98%	91[40.04,141.96]
Nava 1998	0	0	68 (19)		8.19%	68[30.76,105.24]
Troosters 2002	0	0	64 (21)		7.84%	64[22.84,105.16]
Troosters 2010	0	0	48 (31)		6.16%	48[-12.76,108.76]
Total (95% CI)					**100%**	**62.38[38.45,86.31]**
Heterogeneity: Tau²=1460; Chi²=93.49, df=12(P<0.0001); I²=87.16%						
Test for overall effect: Z=5.11(P<0.0001)						

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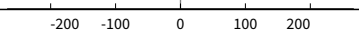
Analysis 1.6. Comparison 1 Rehabilitation versus control, Outcome 6 Change from baseline in shuttle walk test.

Study or subgroup	Rehabilitation N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Greening 2014	0	0	-14 (13)		27.57%	-14[-39.48,11.48]
Man 2004	0	0	74 (21)		24.64%	74[32.84,115.16]
Murphy 2005	0	0	96 (30)		20.88%	96[37.2,154.8]
Seymour 2010	0	0	51 (15)		26.91%	51[21.6,80.4]
Total (95% CI)					**100%**	**48.14[-1.03,97.32]**
Heterogeneity: Tau²=2114.32; Chi²=22.64, df=3(P<0.0001); I²=86.75%						
Test for overall effect: Z=1.92(P=0.06)						



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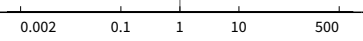
Analysis 1.7. Comparison 1 Rehabilitation versus control, Outcome 7 Subgroup analysis hospital readmission: extensiveness of rehabilitation programme.

Study or subgroup	Pulmonary rehab n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.7.1 Extensive rehab programmes					
Behnke 2000	3/14	9/12		8.77%	0.09[0.01,0.56]
Ko 2011	16/30	13/30		13.96%	1.49[0.54,4.14]
Ko 2016	44/90	63/90		16.84%	0.41[0.22,0.76]
Man 2004	2/20	12/21		9.46%	0.08[0.02,0.45]
Seymour 2010	2/30	10/30		9.89%	0.14[0.03,0.72]
Subtotal (95% CI)	**184**	**183**		**58.92%**	**0.28[0.1,0.78]**
Total events: 67 (Pulmonary rehab), 107 (Control)					
Heterogeneity: Tau²=0.89; Chi²=13.82, df=4(P=0.01); I²=71.06%					
Test for overall effect: Z=2.43(P=0.02)					
1.7.2 Less-extensive rehab programmes					
Eaton 2009	11/47	15/50		14.78%	0.71[0.29,1.77]
Greening 2014	108/169	84/151		17.79%	1.41[0.9,2.21]
Murphy 2005	2/13	5/13		8.52%	0.29[0.04,1.9]
Subtotal (95% CI)	**229**	**214**		**41.08%**	**0.92[0.44,1.93]**
Total events: 121 (Pulmonary rehab), 104 (Control)					
Heterogeneity: Tau²=0.21; Chi²=3.94, df=2(P=0.14); I²=49.18%					
Test for overall effect: Z=0.22(P=0.83)					
Total (95% CI)	**413**	**397**		**100%**	**0.44[0.21,0.91]**
Total events: 188 (Pulmonary rehab), 211 (Control)					
Heterogeneity: Tau²=0.74; Chi²=29.8, df=7(P=0); I²=76.51%					
Test for overall effect: Z=2.2(P=0.03)					
Test for subgroup differences: Chi²=3.4, df=1 (P=0.07), I²=70.58%					



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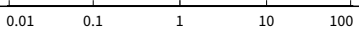
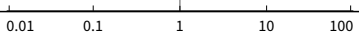
Analysis 1.8. Comparison 1 Rehabilitation versus control, Outcome 8 Subgroup analysis hospital readmission: length of follow-up.

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.8.1 Follow-up >3 months					
Behnke 2000	3/14	9/12		7.86%	0.09[0.01,0.56]
Greening 2014	11/47	15/50		16.09%	0.71[0.29,1.77]
Ko 2011	16/30	13/30		14.77%	1.49[0.54,4.14]
Ko 2016	44/90	63/90		19.77%	0.41[0.22,0.76]
Murphy 2005	2/13	5/13		7.58%	0.29[0.04,1.9]
Subtotal (95% CI)	**194**	**195**		**66.07%**	**0.51[0.24,1.06]**
Total events: 76 (Experimental), 105 (Control)					
Heterogeneity: Tau^2=0.36; Chi^2=9.05, df=4(P=0.06); I^2=55.78%					
Test for overall effect: Z=1.81(P=0.07)					
1.8.2 Follow-up ≤3 months					
Eaton 2009	11/47	15/50		16.09%	0.71[0.29,1.77]
Man 2004	2/20	12/21		8.67%	0.08[0.02,0.45]
Seymour 2010	2/30	10/30		9.17%	0.14[0.03,0.72]
Subtotal (95% CI)	**97**	**101**		**33.93%**	**0.24[0.06,0.98]**
Total events: 15 (Experimental), 37 (Control)					
Heterogeneity: Tau^2=1.08; Chi^2=6.33, df=2(P=0.04); I^2=68.41%					
Test for overall effect: Z=1.98(P=0.05)					
Total (95% CI)	**291**	**296**		**100%**	**0.41[0.22,0.76]**
Total events: 91 (Experimental), 142 (Control)					
Heterogeneity: Tau^2=0.41; Chi^2=16.23, df=7(P=0.02); I^2=56.87%					
Test for overall effect: Z=2.84(P=0)					
Test for subgroup differences: Chi^2=0.87, df=1 (P=0.35), I^2=0%					



Analysis 1.9. Comparison 1 Rehabilitation versus control, Outcome 9 Subgroup analysis hospital readmission: generation of random sequence.

Study or subgroup	Rehabilitation n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.9.1 Low risk of bias					
Eaton 2009	11/47	15/50		14.78%	0.71[0.29,1.77]
Greening 2014	108/169	84/151		17.79%	1.41[0.9,2.21]
Ko 2011	16/30	13/30		13.96%	1.49[0.54,4.14]
Ko 2016	44/90	63/90		16.84%	0.41[0.22,0.76]
Man 2004	2/20	12/21		9.46%	0.08[0.02,0.45]
Seymour 2010	2/30	10/30		9.89%	0.14[0.03,0.72]
Subtotal (95% CI)	**386**	**372**		**82.72%**	**0.55[0.25,1.19]**
Total events: 183 (Rehabilitation), 197 (Control)					
Heterogeneity: Tau^2=0.66; Chi^2=23.5, df=5(P=0); I^2=78.72%					
Test for overall effect: Z=1.52(P=0.13)					
1.9.2 Unclear or high risk of bias					
Behnke 2000	3/14	9/12		8.77%	0.09[0.01,0.56]
Murphy 2005	2/13	5/13		8.52%	0.29[0.04,1.9]



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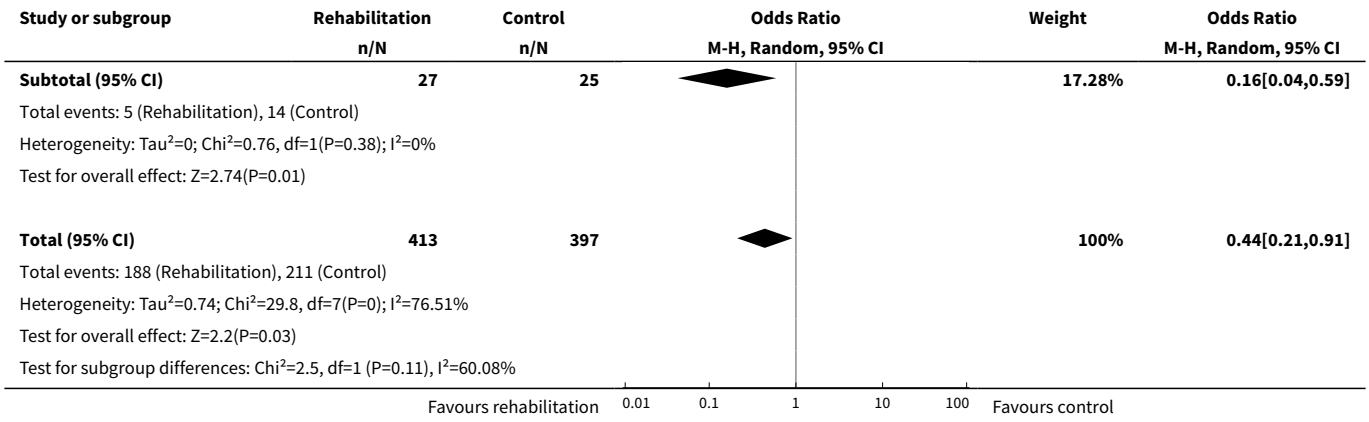
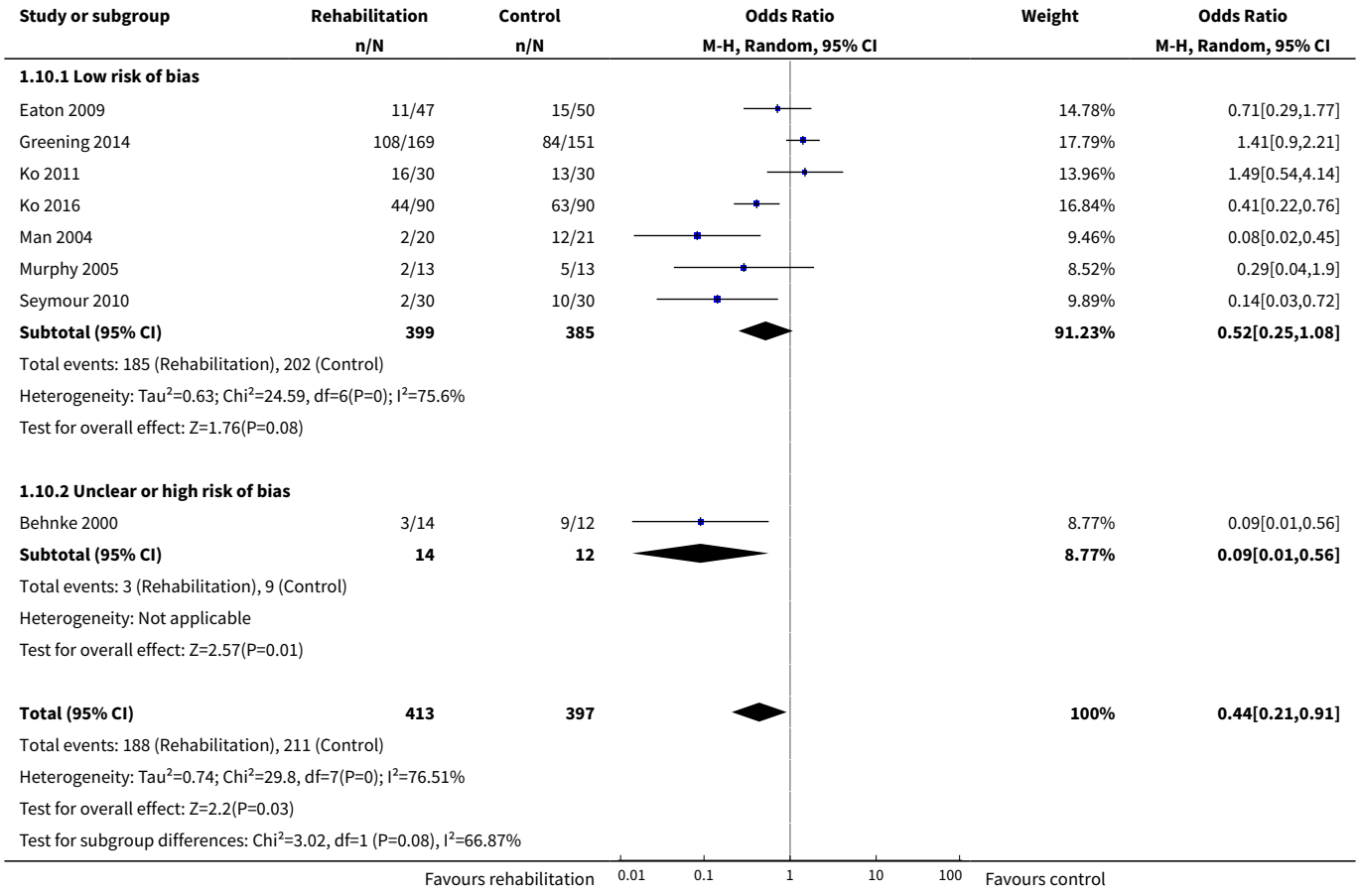


Analysis 1.10. Comparison 1 Rehabilitation versus control, Outcome 10 Subgroup analysis hospital readmission: concealment of random allocation.



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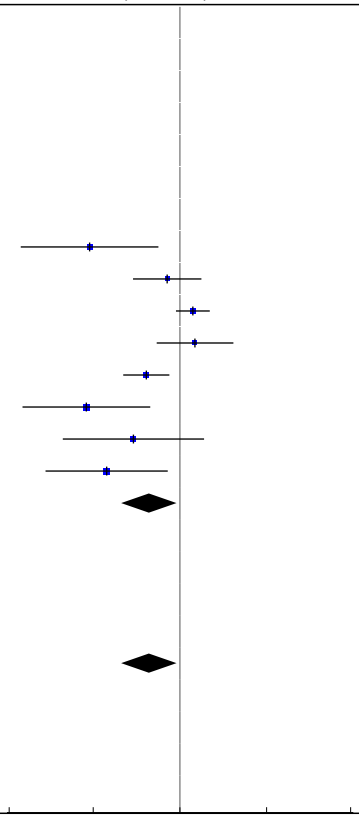
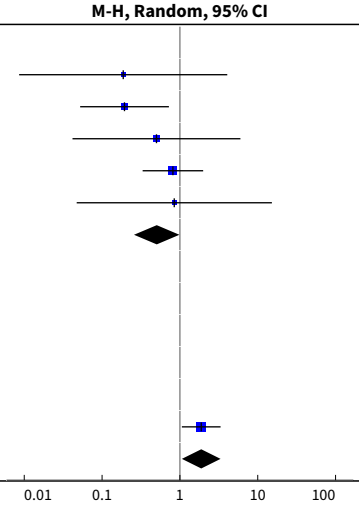
Analysis 1.11. Comparison 1 Rehabilitation versus control, Outcome 11 Subgroup analysis hospital readmission: blinding.

Study or subgroup	Rehabilitation n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.11.1 Low risk of bias					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Rehabilitation), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.11.2 Unclear or high risk of bias					
Behnke 2000	3/14	9/12		8.77%	0.09[0.01,0.56]
Eaton 2009	11/47	15/50		14.78%	0.71[0.29,1.77]
Greening 2014	108/169	84/151		17.79%	1.41[0.9,2.21]
Ko 2011	16/30	13/30		13.96%	1.49[0.54,4.14]
Ko 2016	44/90	63/90		16.84%	0.41[0.22,0.76]
Man 2004	2/20	12/21		9.46%	0.08[0.02,0.45]
Murphy 2005	2/13	5/13		8.52%	0.29[0.04,1.9]
Seymour 2010	2/30	10/30		9.89%	0.14[0.03,0.72]
Subtotal (95% CI)	**413**	**397**		**100%**	**0.44[0.21,0.91]**
Total events: 188 (Rehabilitation), 211 (Control)					
Heterogeneity: Tau^2=0.74; Chi^2=29.8, df=7(P=0); I^2=76.51%					
Test for overall effect: Z=2.2(P=0.03)					
Total (95% CI)	**413**	**397**		**100%**	**0.44[0.21,0.91]**
Total events: 188 (Rehabilitation), 211 (Control)					
Heterogeneity: Tau^2=0.74; Chi^2=29.8, df=7(P=0); I^2=76.51%					
Test for overall effect: Z=2.2(P=0.03)					
Test for subgroup differences: Not applicable					



Analysis 1.12. Comparison 1 Rehabilitation versus control, Outcome 12 Subgroup analysis mortality: extensiveness of rehabilitation programme.

Study or subgroup	Pulmonary rehab n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.12.1 Extensive rehab programmes					
Ko 2011	0/30	2/30		6.79%	0.19[0.01,4.06]
Troosters 2002	6/24	12/19		19.91%	0.19[0.05,0.72]
Man 2004	1/20	2/21		9.45%	0.5[0.04,5.99]
Ko 2016	10/90	12/90		25.83%	0.81[0.33,1.99]
Behnke 2000	1/14	1/12		7.53%	0.85[0.05,15.16]
Subtotal (95% CI)	**178**	**172**		**69.51%**	**0.5[0.26,0.99]**
Total events: 18 (Pulmonary rehab), 29 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.64, df=4(P=0.46); I^2=0%					
Test for overall effect: Z=2(P=0.05)					
1.12.2 Less-extensive rehab programmes					
Greening 2014	41/169	22/151		30.49%	1.88[1.06,3.33]
Subtotal (95% CI)	**169**	**151**		**30.49%**	**1.88[1.06,3.33]**



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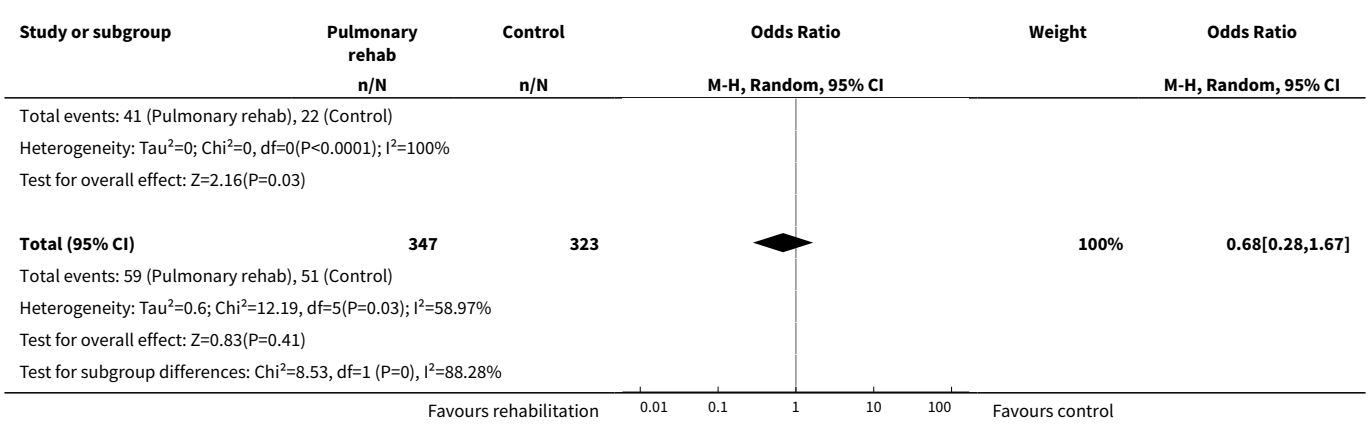
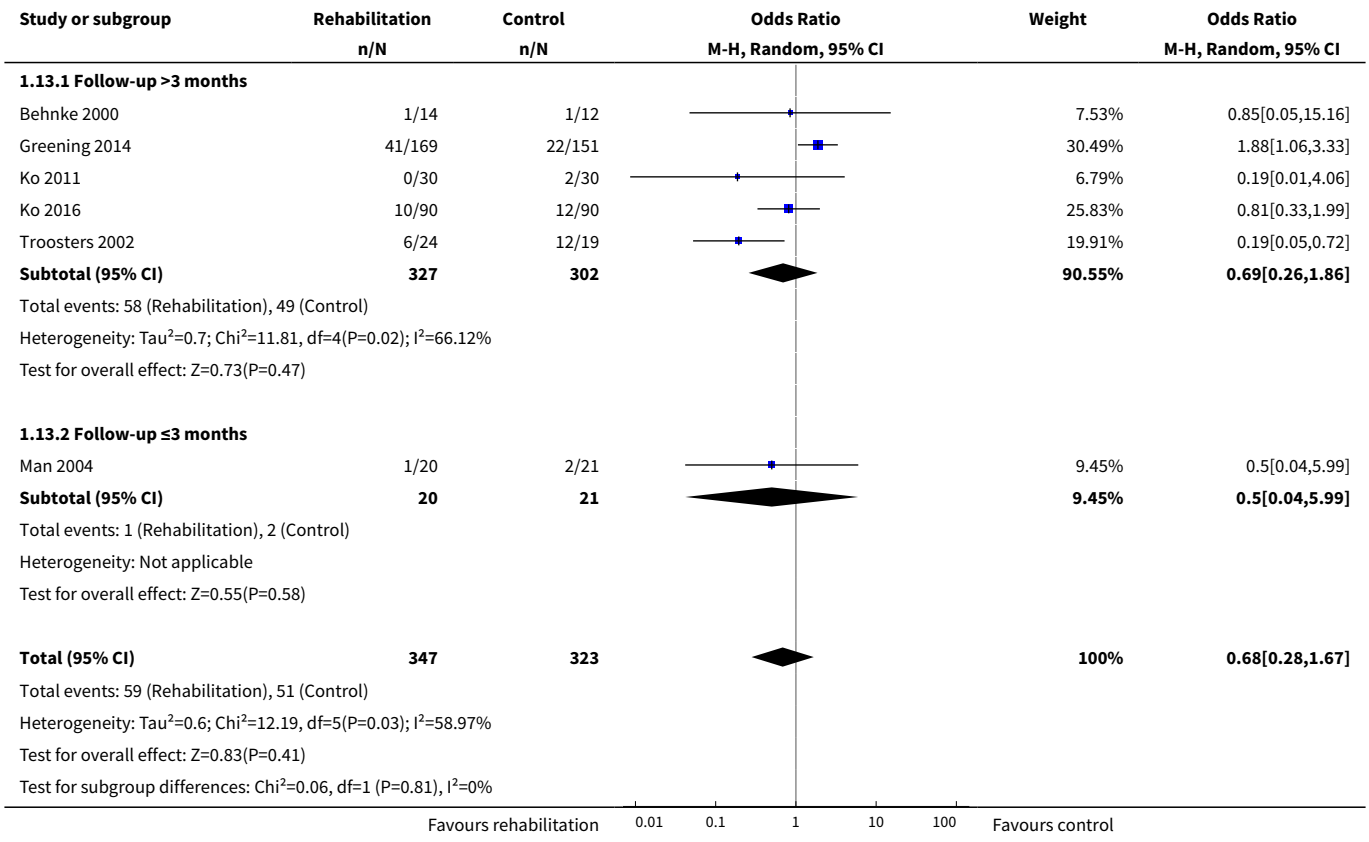


Analysis 1.13. Comparison 1 Rehabilitation versus control, Outcome 13 Subgroup analysis mortality: length of follow-up.



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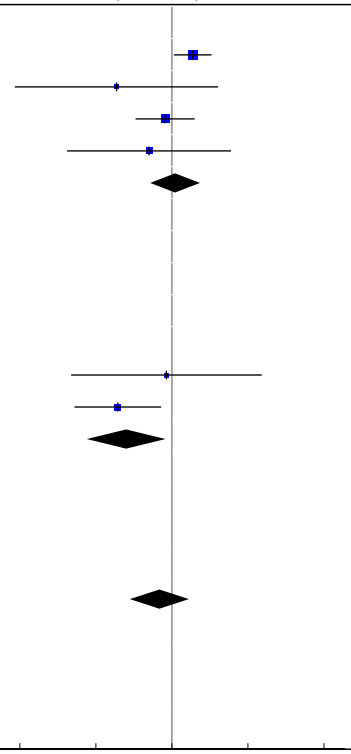
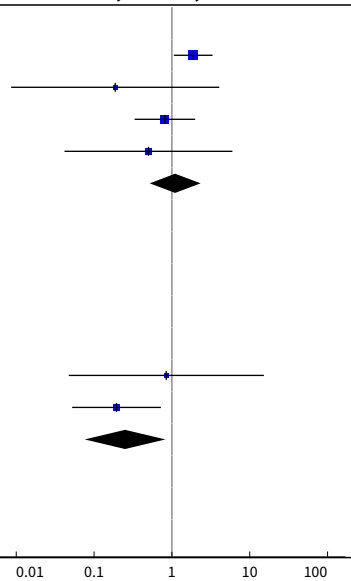
Analysis 1.14. Comparison 1 Rehabilitation versus control, Outcome 14 Subgroup analysis mortality: generation of random sequence.

Study or subgroup	Rehabilitation n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.14.1 Low risk of bias					
Greening 2014	41/169	22/151		30.49%	1.88[1.06,3.33]
Ko 2011	0/30	2/30		6.79%	0.19[0.01,4.06]
Ko 2016	10/90	12/90		25.83%	0.81[0.33,1.99]
Man 2004	1/20	2/21		9.45%	0.5[0.04,5.99]
Subtotal (95% CI)	**309**	**292**		**72.56%**	**1.1[0.52,2.34]**
Total events: 52 (Rehabilitation), 38 (Control)					
Heterogeneity: Tau^2=0.21; Chi^2=4.72, df=3(P=0.19); I^2=36.42%					
Test for overall effect: Z=0.25(P=0.8)					
1.14.2 Unclear or high risk of bias					
Behnke 2000	1/14	1/12		7.53%	0.85[0.05,15.16]
Troosters 2002	6/24	12/19		19.91%	0.19[0.05,0.72]
Subtotal (95% CI)	**38**	**31**		**27.44%**	**0.25[0.08,0.83]**
Total events: 7 (Rehabilitation), 13 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.83, df=1(P=0.36); I^2=0%					
Test for overall effect: Z=2.27(P=0.02)					
Total (95% CI)	**347**	**323**		**100%**	**0.68[0.28,1.67]**
Total events: 59 (Rehabilitation), 51 (Control)					
Heterogeneity: Tau^2=0.6; Chi^2=12.19, df=5(P=0.03); I^2=58.97%					
Test for overall effect: Z=0.83(P=0.41)					
Test for subgroup differences: Chi^2=4.23, df=1 (P=0.04), I^2=76.38%					



Analysis 1.15. Comparison 1 Rehabilitation versus control, Outcome 15 Subgroup analysis mortality: concealment of random allocation.

Study or subgroup	Rehabilitation n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.15.1 Low risk of bias					
Greening 2014	41/169	22/151		30.49%	1.88[1.06,3.33]
Ko 2011	0/30	2/30		6.79%	0.19[0.01,4.06]
Ko 2016	10/90	12/90		25.83%	0.81[0.33,1.99]
Man 2004	1/20	2/21		9.45%	0.5[0.04,5.99]
Subtotal (95% CI)	**309**	**292**		**72.56%**	**1.1[0.52,2.34]**
Total events: 52 (Rehabilitation), 38 (Control)					
Heterogeneity: Tau^2=0.21; Chi^2=4.72, df=3(P=0.19); I^2=36.42%					
Test for overall effect: Z=0.25(P=0.8)					
1.15.2 Unclear or high risk of bias					
Behnke 2000	1/14	1/12		7.53%	0.85[0.05,15.16]
Troosters 2002	6/24	12/19		19.91%	0.19[0.05,0.72]
Subtotal (95% CI)	**38**	**31**		**27.44%**	**0.25[0.08,0.83]**
Total events: 7 (Rehabilitation), 13 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.83, df=1(P=0.36); I^2=0%					
Test for overall effect: Z=2.27(P=0.02)					



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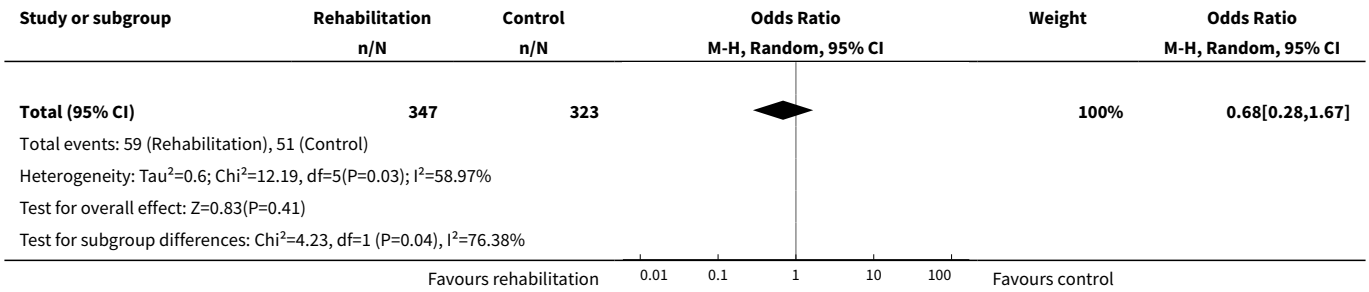
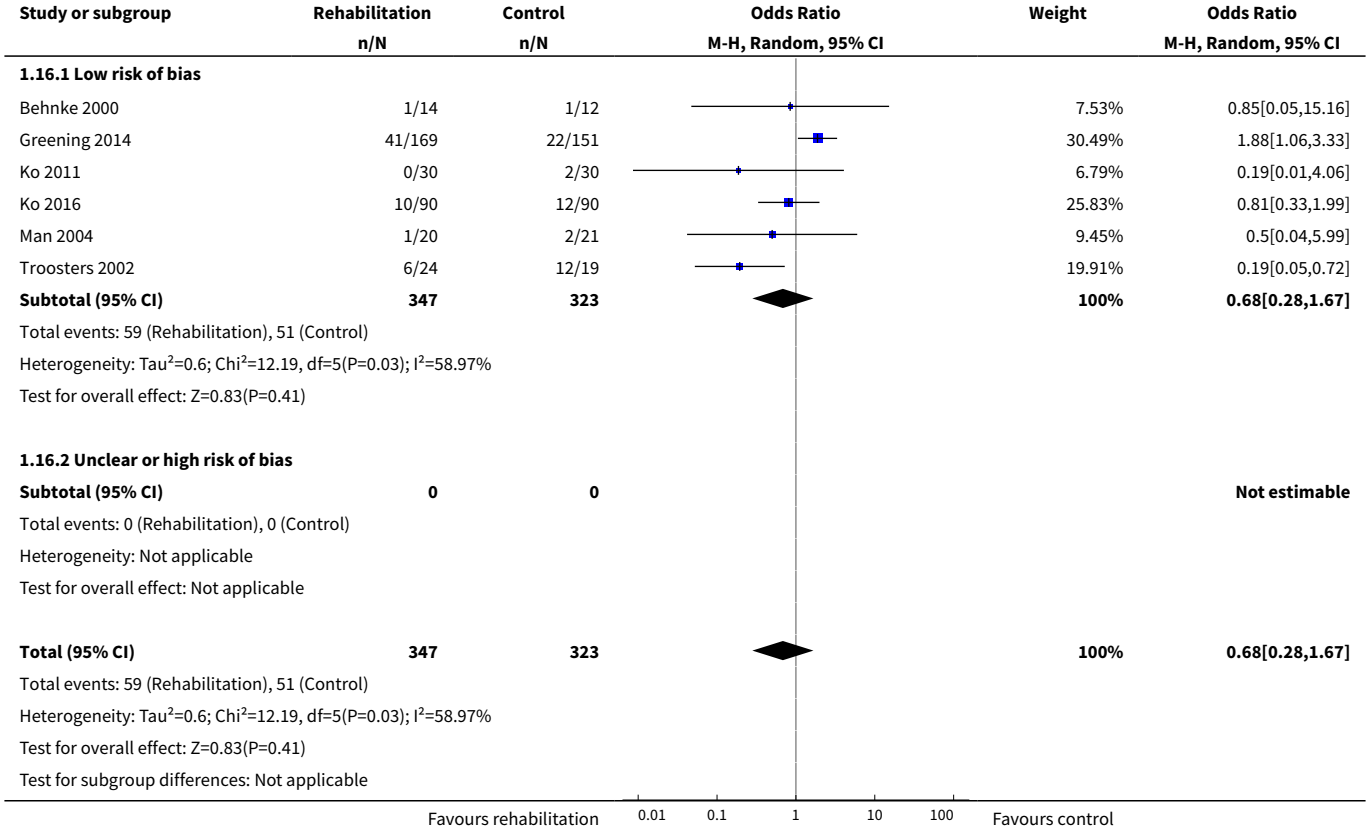
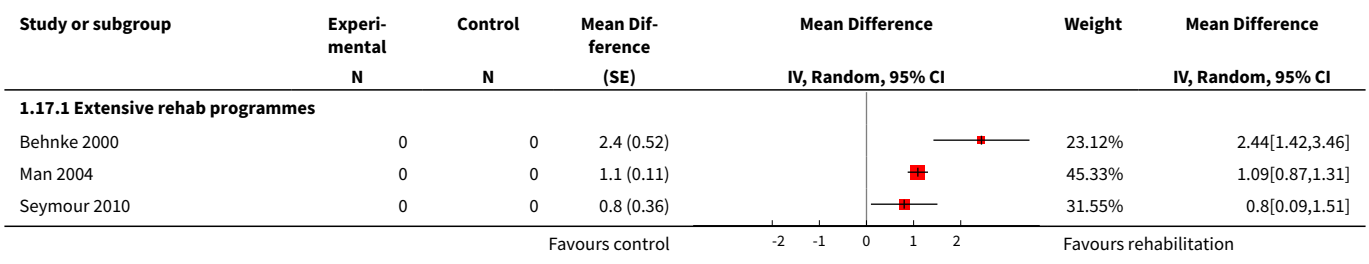


Analysis 1.16. Comparison 1 Rehabilitation versus control, Outcome 16 Subgroup analysis mortality: blinding.



Analysis 1.17. Comparison 1 Rehabilitation versus control, Outcome 17 Subgroup analysis CRQ dyspnoea domain: extensiveness of rehabilitation programme.



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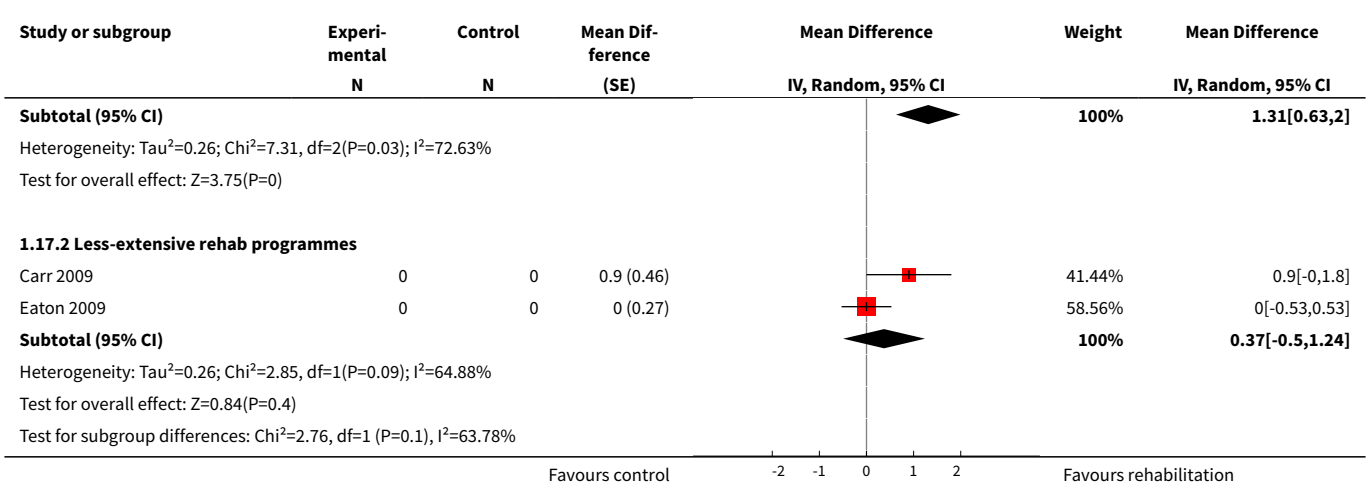
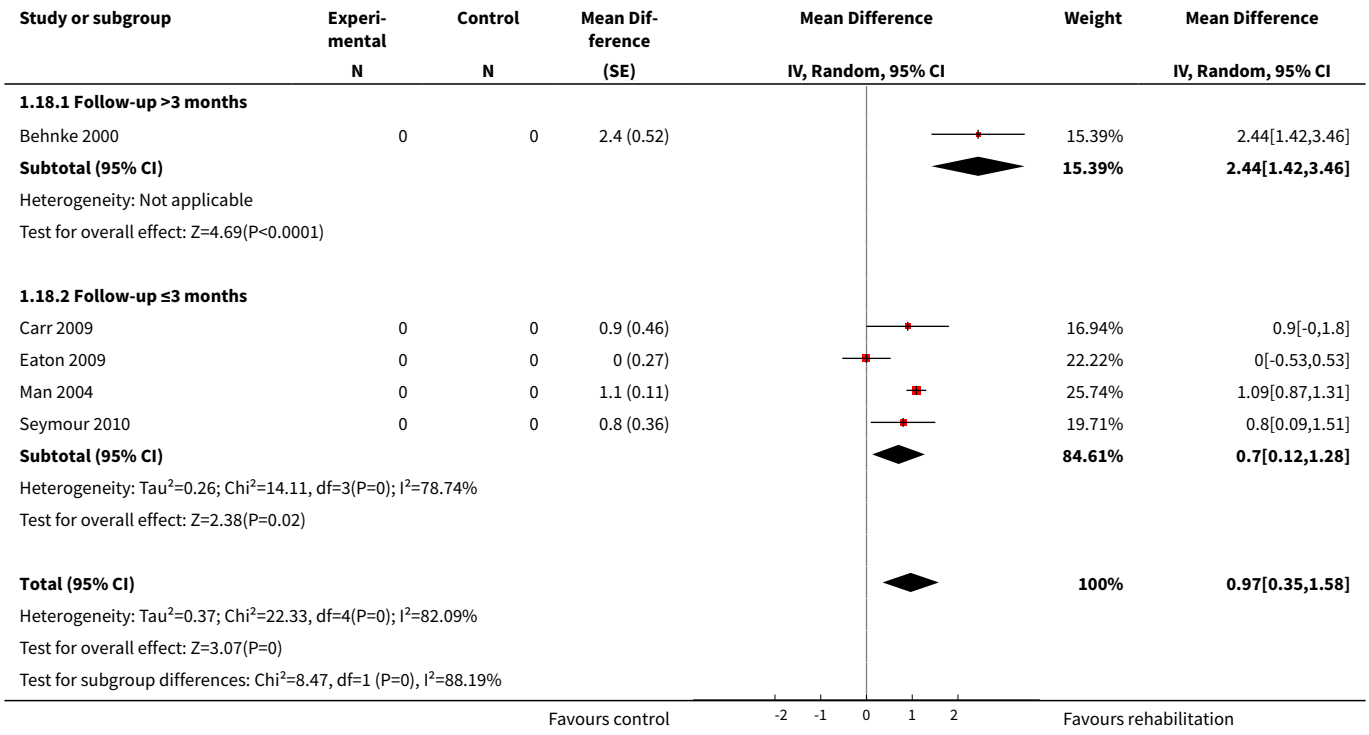


Analysis 1.18. Comparison 1 Rehabilitation versus control, Outcome 18 Subgroup analysis CRQ dyspnoea domain: length of follow-up.



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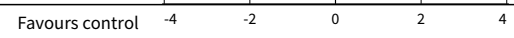
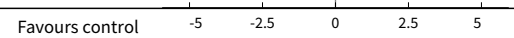
Analysis 1.19. Comparison 1 Rehabilitation versus control, Outcome 19 Subgroup analysis CRQ dyspnoea domain: generation of random sequence.

Study or subgroup	Rehabilitation N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.19.1 Low risk of bias						
Eaton 2009	0	0	0 (0.27)		22.22%	0[-0.53,0.53]
Man 2004	0	0	1.1 (0.11)		25.74%	1.09[0.87,1.31]
Seymour 2010	0	0	0.8 (0.36)		19.71%	0.8[0.09,1.51]
Subtotal (95% CI)					**67.67%**	**0.65[-0.07,1.37]**
Heterogeneity: Tau^2=0.34; Chi^2=14.11, df=2(P=0); I^2=85.82%						
Test for overall effect: Z=1.78(P=0.08)						
1.19.2 Unclear or high risk of bias						
Behnke 2000	0	0	2.4 (0.52)		15.39%	2.44[1.42,3.46]
Carr 2009	0	0	0.9 (0.46)		16.94%	0.9[-0,1.8]
Subtotal (95% CI)					**32.33%**	**1.65[0.14,3.16]**
Heterogeneity: Tau^2=0.94; Chi^2=4.92, df=1(P=0.03); I^2=79.68%						
Test for overall effect: Z=2.14(P=0.03)						
Total (95% CI)					**100%**	**0.97[0.35,1.58]**
Heterogeneity: Tau^2=0.37; Chi^2=22.33, df=4(P=0); I^2=82.09%						
Test for overall effect: Z=3.07(P=0)						
Test for subgroup differences: Chi^2=1.38, df=1 (P=0.24), I^2=27.56%						



Analysis 1.20. Comparison 1 Rehabilitation versus control, Outcome 20 Subgroup analysis CRQ dyspnoea domain: concealment of random allocation.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.20.1 Low risk of bias						
Eaton 2009	0	0	0 (0.27)		22.22%	0[-0.53,0.53]
Man 2004	0	0	1.1 (0.11)		25.74%	1.09[0.87,1.31]
Seymour 2010	0	0	0.8 (0.36)		19.71%	0.8[0.09,1.51]
Subtotal (95% CI)					**67.67%**	**0.65[-0.07,1.37]**
Heterogeneity: Tau^2=0.34; Chi^2=14.11, df=2(P=0); I^2=85.82%						
Test for overall effect: Z=1.78(P=0.08)						
1.20.2 Unclear or high risk of bias						
Behnke 2000	0	0	2.4 (0.52)		15.39%	2.44[1.42,3.46]
Carr 2009	0	0	0.9 (0.46)		16.94%	0.9[-0,1.8]
Subtotal (95% CI)					**32.33%**	**1.65[0.14,3.16]**
Heterogeneity: Tau^2=0.94; Chi^2=4.92, df=1(P=0.03); I^2=79.68%						
Test for overall effect: Z=2.14(P=0.03)						
Total (95% CI)					**100%**	**0.97[0.35,1.58]**
Heterogeneity: Tau^2=0.37; Chi^2=22.33, df=4(P=0); I^2=82.09%						
Test for overall effect: Z=3.07(P=0)						
Test for subgroup differences: Chi^2=1.38, df=1 (P=0.24), I^2=27.56%						



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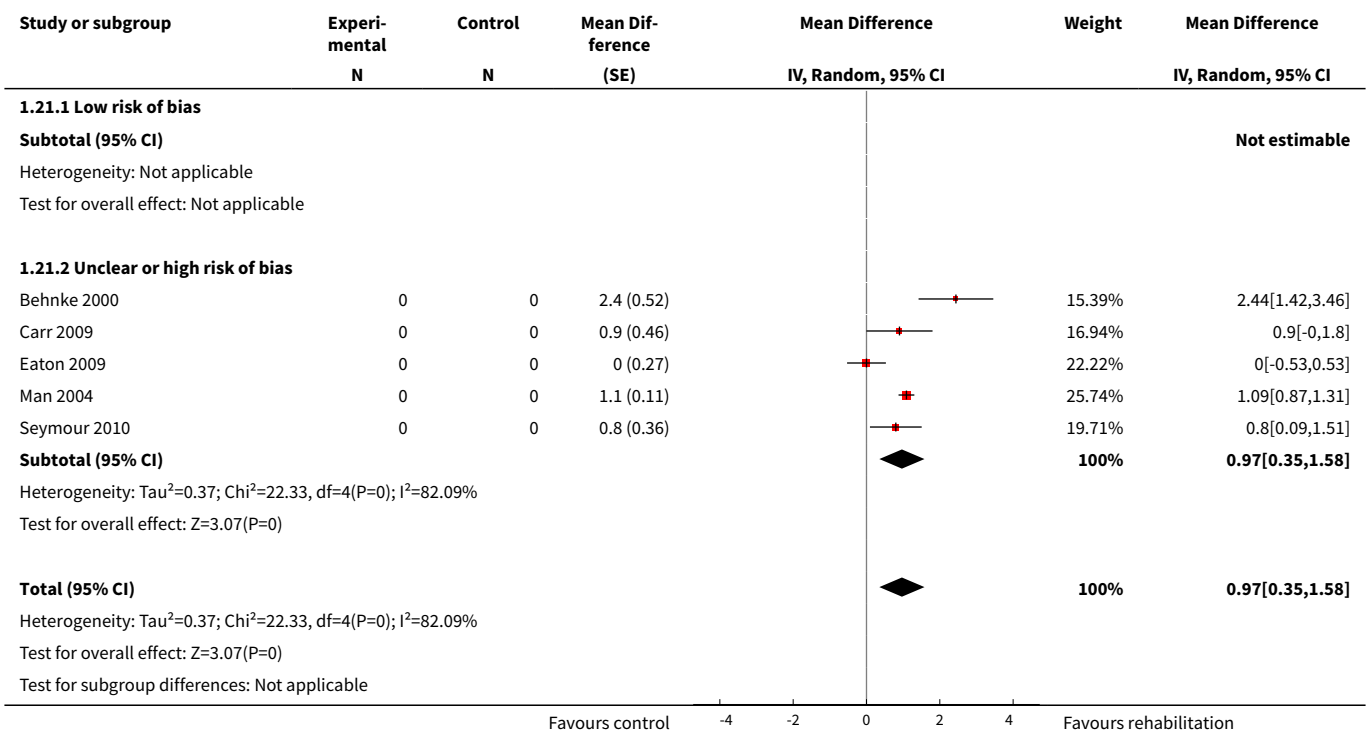
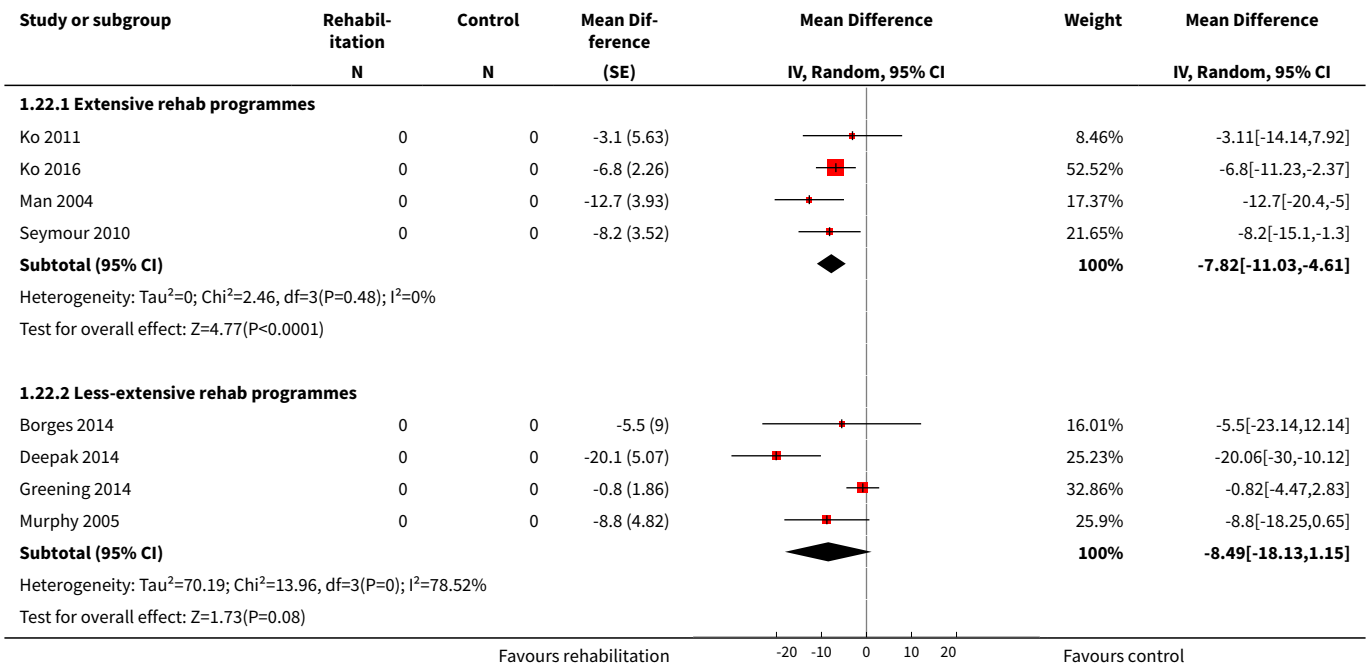
Analysis 1.21. Comparison 1 Rehabilitation versus control, Outcome 21 Subgroup analysis CRQ dyspnoea domain: blinding.



Analysis 1.22. Comparison 1 Rehabilitation versus control, Outcome 22 Subgroup analysis SGRQ total score: extensiveness of rehabilitation programme.



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Study or subgroup	Rehabilitation N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Test for subgroup differences: Chi²=0.02, df=1 (P=0.9), I²=0%						

Favours rehabilitation -20 -10 0 10 20 Favours control

Analysis 1.23. Comparison 1 Rehabilitation versus control, Outcome 23 Subgroup analysis SGRQ total score: length of follow-up.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.23.1 Follow-up >3 months						
Greening 2014	0	0	-0.8 (1.86)		19.39%	-0.82[-4.47,2.83]
Ko 2011	0	0	-3.1 (5.63)		9.12%	-3.11[-14.14,7.92]
Ko 2016	0	0	-6.8 (2.26)		18.19%	-6.8[-11.23,-2.37]
Murphy 2005	0	0	-8.8 (4.82)		10.85%	-8.8[-18.25,0.65]
Subtotal (95% CI)					**57.55%**	**-4.27[-8.32,-0.22]**
Heterogeneity: Tau²=7.16; Chi²=5.41, df=3(P=0.14); I²=44.53%						
Test for overall effect: Z=2.07(P=0.04)						
1.23.2 Follow-up ≤3 months						
Borges 2014	0	0	-5.5 (9)		4.74%	-5.5[-23.14,12.14]
Deepak 2014	0	0	-20.1 (5.07)		10.28%	-20.06[-30,-10.12]
Man 2004	0	0	-12.7 (3.93)		13.12%	-12.7[-20.4,-5]
Seymour 2010	0	0	-8.2 (3.52)		14.3%	-8.2[-15.1,-1.3]
Subtotal (95% CI)					**42.45%**	**-12.09[-17.61,-6.57]**
Heterogeneity: Tau²=9.28; Chi²=4.24, df=3(P=0.24); I²=29.28%						
Test for overall effect: Z=4.3(P<0.0001)						
Total (95% CI)					**100%**	**-7.8[-12.12,-3.47]**
Heterogeneity: Tau²=21.64; Chi²=19.44, df=7(P=0.01); I²=63.99%						
Test for overall effect: Z=3.53(P=0)						
Test for subgroup differences: Chi²=5.01, df=1 (P=0.03), I²=80.06%						

Favours rehabilitation -100 -50 0 50 100 Favours control

Analysis 1.24. Comparison 1 Rehabilitation versus control, Outcome 24 Subgroup analysis SGRQ total score: generation of random sequence.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.24.1 Low risk of bias						
Borges 2014	0	0	-5.5 (9)		4.74%	-5.5[-23.14,12.14]
Greening 2014	0	0	-0.8 (1.86)		19.39%	-0.82[-4.47,2.83]
Ko 2011	0	0	-3.1 (5.63)		9.12%	-3.11[-14.14,7.92]
Ko 2016	0	0	-6.8 (2.26)		18.19%	-6.8[-11.23,-2.37]
Man 2004	0	0	-12.7 (3.93)		13.12%	-12.7[-20.4,-5]
Seymour 2010	0	0	-8.2 (3.52)		14.3%	-8.2[-15.1,-1.3]

Favours rehabilitation -100 -50 0 50 100 Favours control

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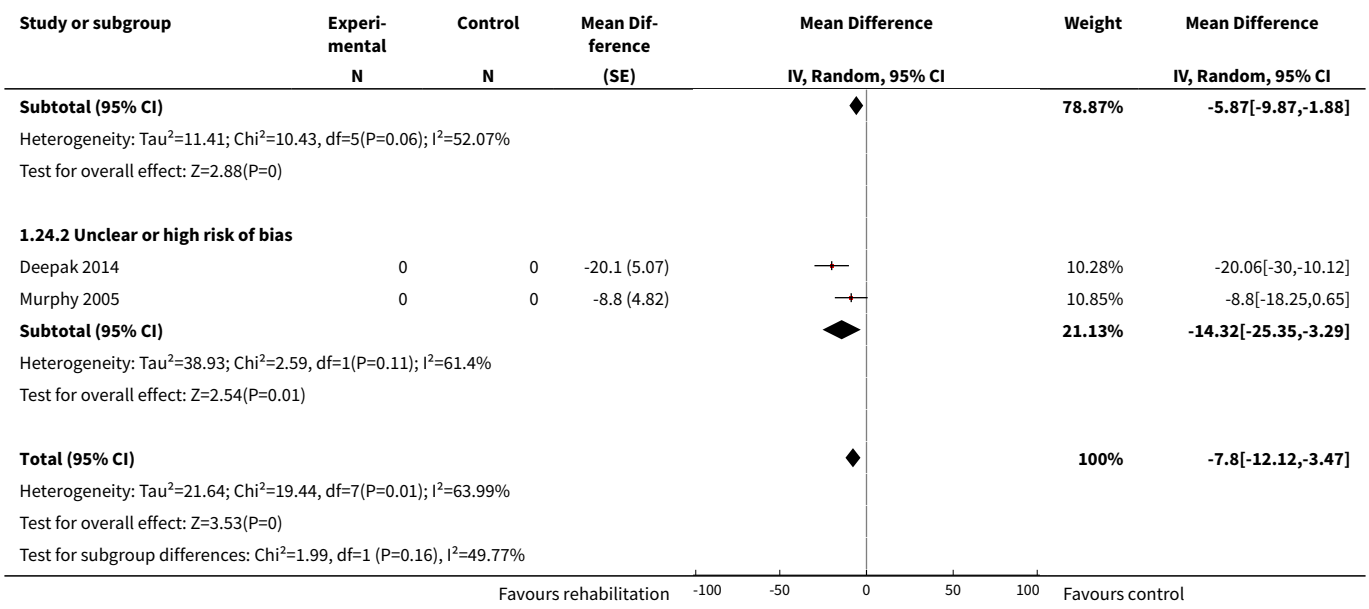
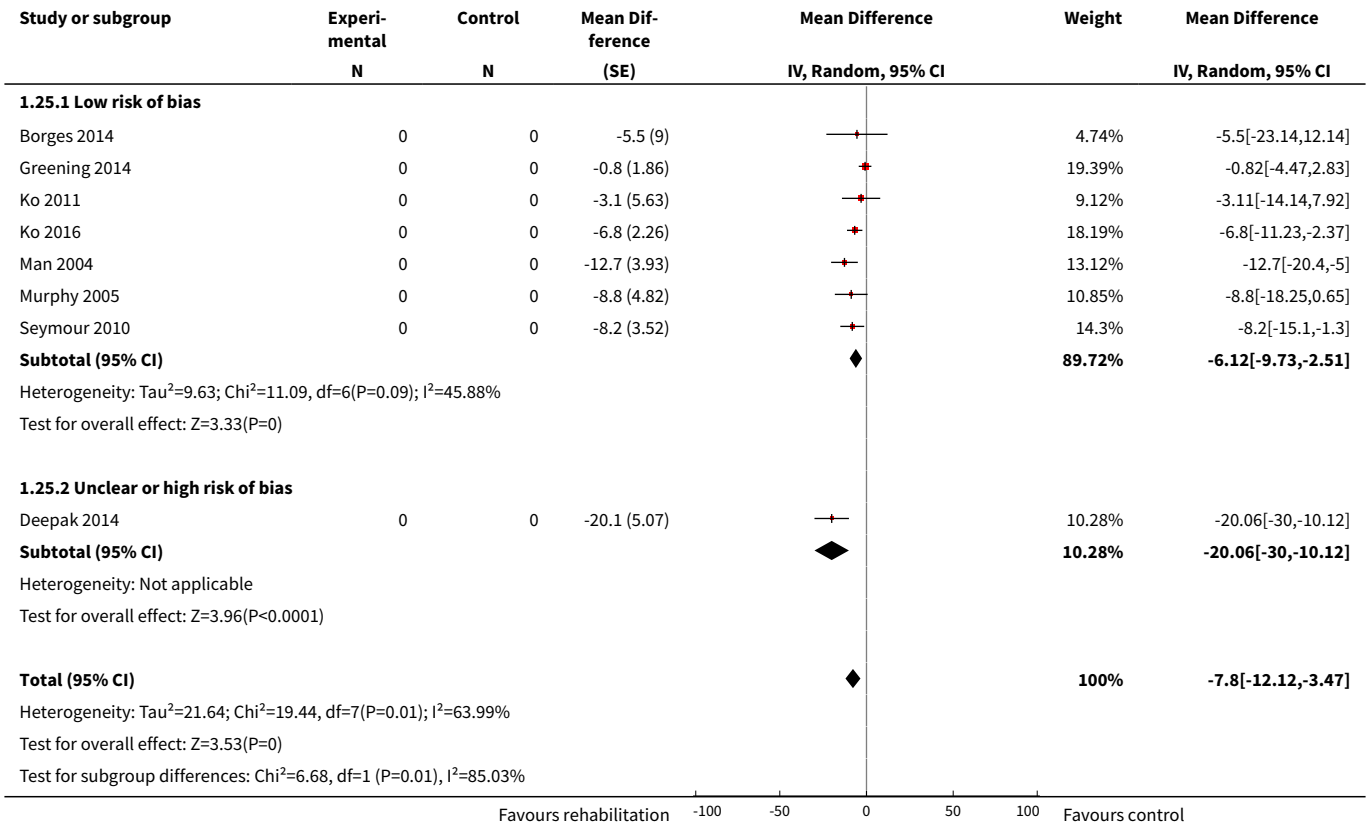


Analysis 1.25. Comparison 1 Rehabilitation versus control, Outcome 25 Subgroup analysis SGRQ total score: concealment of random allocation.



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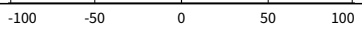
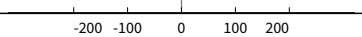
Analysis 1.26. Comparison 1 Rehabilitation versus control, Outcome 26 Subgroup analysis SGRQ total score: blinding.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.26.1 Low risk of bias						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.26.2 Unclear or high risk of bias						
Borges 2014	0	0	-5.5 (9)		4.74%	-5.5[-23.14,12.14]
Deepak 2014	0	0	-20.1 (5.07)		10.28%	-20.06[-30,-10.12]
Greening 2014	0	0	-0.8 (1.86)		19.39%	-0.82[-4.47,2.83]
Ko 2011	0	0	-3.1 (5.63)		9.12%	-3.11[-14.14,7.92]
Ko 2016	0	0	-6.8 (2.26)		18.19%	-6.8[-11.23,-2.37]
Man 2004	0	0	-12.7 (3.93)		13.12%	-12.7[-20.4,-5]
Murphy 2005	0	0	-8.8 (4.82)		10.85%	-8.8[-18.25,0.65]
Seymour 2010	0	0	-8.2 (3.52)		14.3%	-8.2[-15.1,-1.3]
Subtotal (95% CI)					**100%**	**-7.8[-12.12,-3.47]**
Heterogeneity: Tau^2=21.64; Chi^2=19.44, df=7(P=0.01); I^2=63.99%						
Test for overall effect: Z=3.53(P=0)						
Total (95% CI)					**100%**	**-7.8[-12.12,-3.47]**
Heterogeneity: Tau^2=21.64; Chi^2=19.44, df=7(P=0.01); I^2=63.99%						
Test for overall effect: Z=3.53(P=0)						
Test for subgroup differences: Not applicable						



Analysis 1.27. Comparison 1 Rehabilitation versus control, Outcome 27 Subgroup analysis 6-minute walking test: extensiveness of rehabilitation programme.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.27.1 Extensive rehab programmes						
Behnke 2000	0	0	215 (28)		7.05%	215[160.12,269.88]
He 2015	0	0	39 (3)		10.79%	39[33.12,44.88]
Ko 2011	0	0	34 (25)		7.59%	34[-15,83]
Ko 2016	0	0	12.5 (10.45)		10.1%	12.5[-7.98,32.98]
Nava 1998	0	0	68 (19)		8.7%	68[30.76,105.24]
Troosters 2002	0	0	64 (21)		8.33%	64[22.84,105.16]
Subtotal (95% CI)					**52.57%**	**65.5[31.71,99.3]**
Heterogeneity: Tau^2=1436; Chi^2=49.63, df=5(P<0.0001); I^2=89.93%						
Test for overall effect: Z=3.8(P=0)						
1.27.2 Less-extensive rehab programmes						
Borges 2014	0	0	111 (34)		6.05%	111[44.36,177.64]
Carr 2009	0	0	-25 (23)		7.96%	-25[-70.08,20.08]
Deepak 2014	0	0	66 (15)		9.4%	66[36.6,95.4]
Eaton 2009	0	0	-2 (16)		9.23%	-2[-33.36,29.36]



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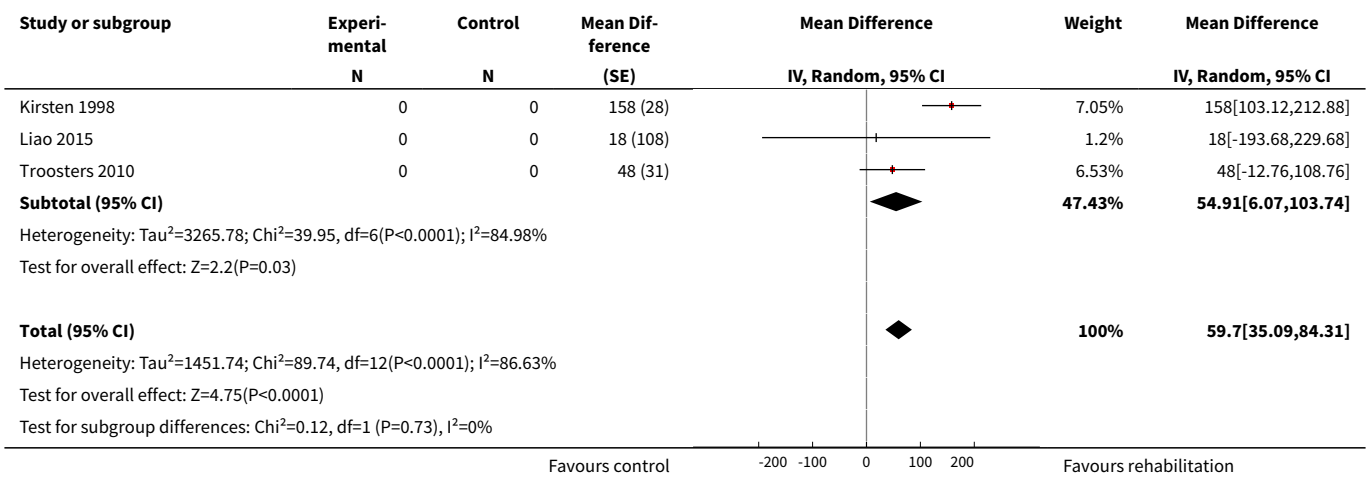
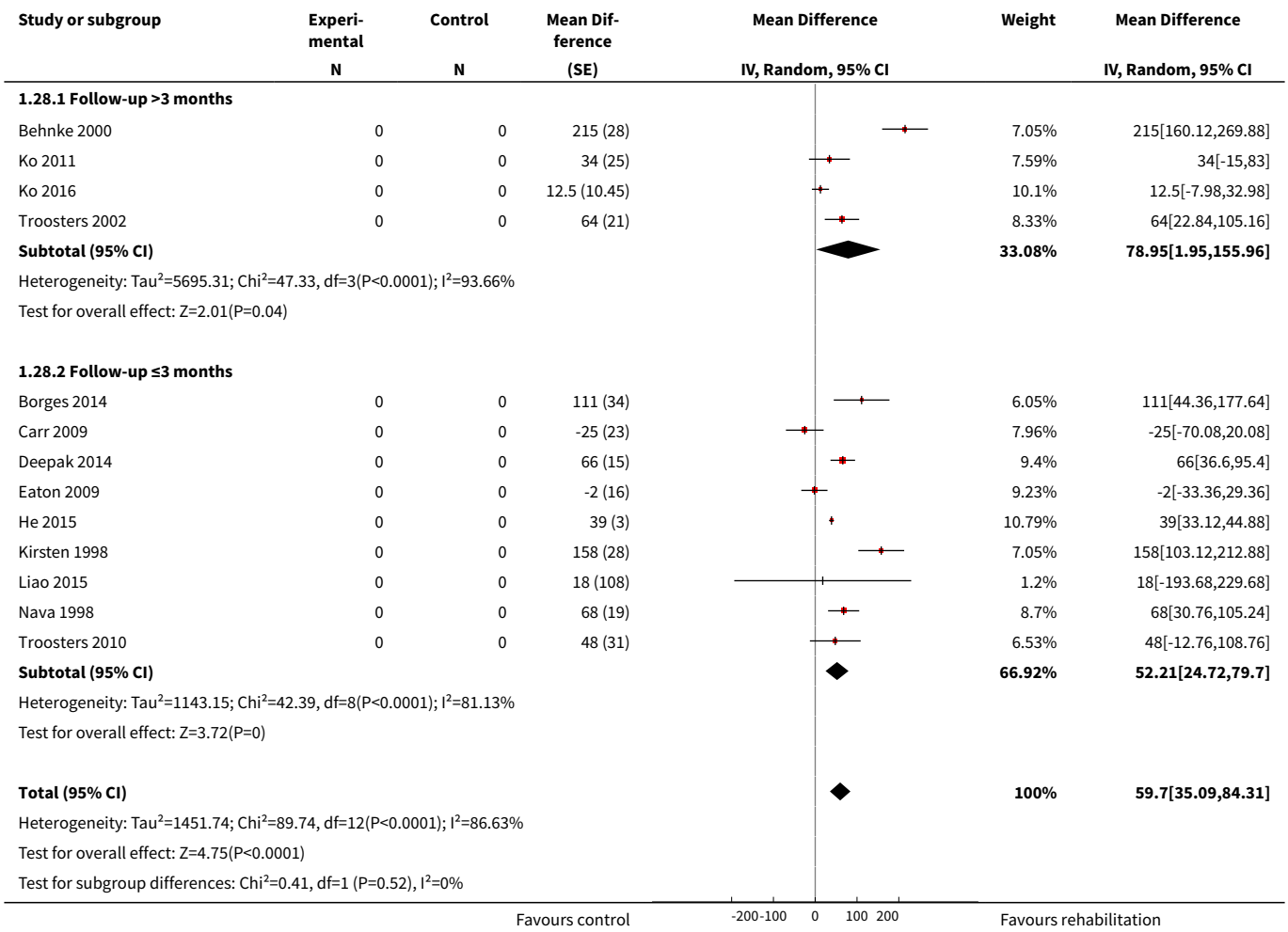


Analysis 1.28. Comparison 1 Rehabilitation versus control, Outcome 28 Subgroup analysis 6-minute walk test: length of follow-up.



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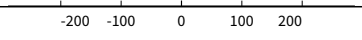
Analysis 1.29. Comparison 1 Rehabilitation versus control, Outcome 29 Subgroup analysis 6-minute walk test: generation of random sequence.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.29.1 Low risk of bias						
Borges 2014	0	0	111 (34)		6.05%	111[44.36,177.64]
Eaton 2009	0	0	-2 (16)		9.23%	-2[-33.36,29.36]
He 2015	0	0	39 (3)		10.79%	39[33.12,44.88]
Ko 2011	0	0	34 (25)		7.59%	34[-15,83]
Ko 2016	0	0	12.5 (10.45)		10.1%	12.5[-7.98,32.98]
Liao 2015	0	0	18 (108)		1.2%	18[-193.68,229.68]
Nava 1998	0	0	68 (19)		8.7%	68[30.76,105.24]
Subtotal (95% CI)					**53.67%**	**34.89[14.17,55.61]**
Heterogeneity: Tau^2=400.08; Chi^2=19.33, df=6(P=0); I^2=68.95%						
Test for overall effect: Z=3.3(P=0)						
1.29.2 Unclear or high risk of bias						
Behnke 2000	0	0	215 (28)		7.05%	215[160.12,269.88]
Carr 2009	0	0	-25 (23)		7.96%	-25[-70.08,20.08]
Deepak 2014	0	0	66 (15)		9.4%	66[36.6,95.4]
Kirsten 1998	0	0	158 (28)		7.05%	158[103.12,212.88]
Troosters 2002	0	0	64 (21)		8.33%	64[22.84,105.16]
Troosters 2010	0	0	48 (31)		6.53%	48[-12.76,108.76]
Subtotal (95% CI)					**46.33%**	**86.44[25.63,147.24]**
Heterogeneity: Tau^2=5164.62; Chi^2=54.08, df=5(P<0.0001); I^2=90.75%						
Test for overall effect: Z=2.79(P=0.01)						
Total (95% CI)					**100%**	**59.7[35.09,84.31]**
Heterogeneity: Tau^2=1451.74; Chi^2=89.74, df=12(P<0.0001); I^2=86.63%						
Test for overall effect: Z=4.75(P<0.0001)						
Test for subgroup differences: Chi^2=2.47, df=1 (P=0.12), I^2=59.57%						



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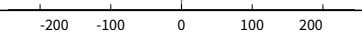
Analysis 1.30. Comparison 1 Rehabilitation versus control, Outcome 30 Subgroup analysis 6-minute walk test: concealment of random allocation.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.30.1 Low risk of bias						
Borges 2014	0	0	111 (34)		5.7%	111[44.36,177.64]
Eaton 2009	0	0	-2 (16)		8.69%	-2[-33.36,29.36]
He 2015	0	0	39 (3)		10.15%	39[33.12,44.88]
Ko 2011	0	0	34 (25)		7.15%	34[-15,83]
Ko 2016	0	0	12.5 (10.45)		9.5%	12.5[-7.98,32.98]
Subtotal (95% CI)					**41.19%**	**29.55[6.15,52.95]**
Heterogeneity: Tau^2=443.2; Chi^2=16.56, df=4(P=0); I^2=75.85%						
Test for overall effect: Z=2.47(P=0.01)						
1.30.2 Unclear or high risk of bias						



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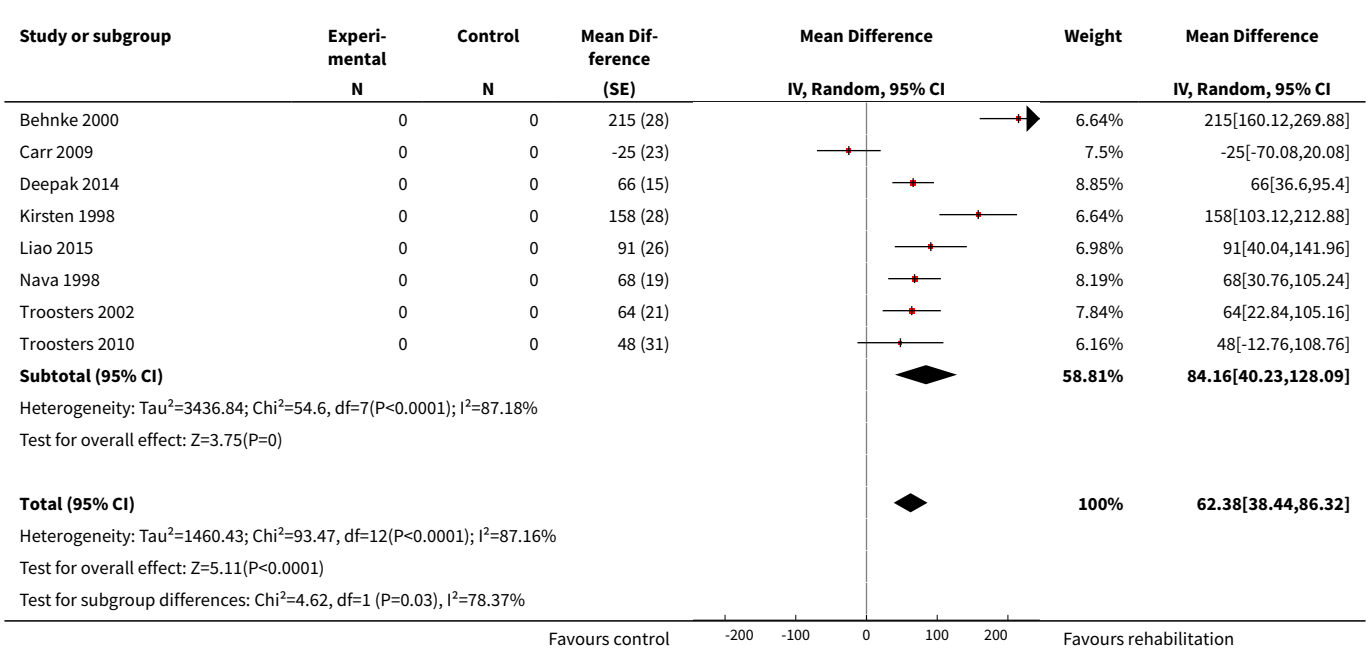
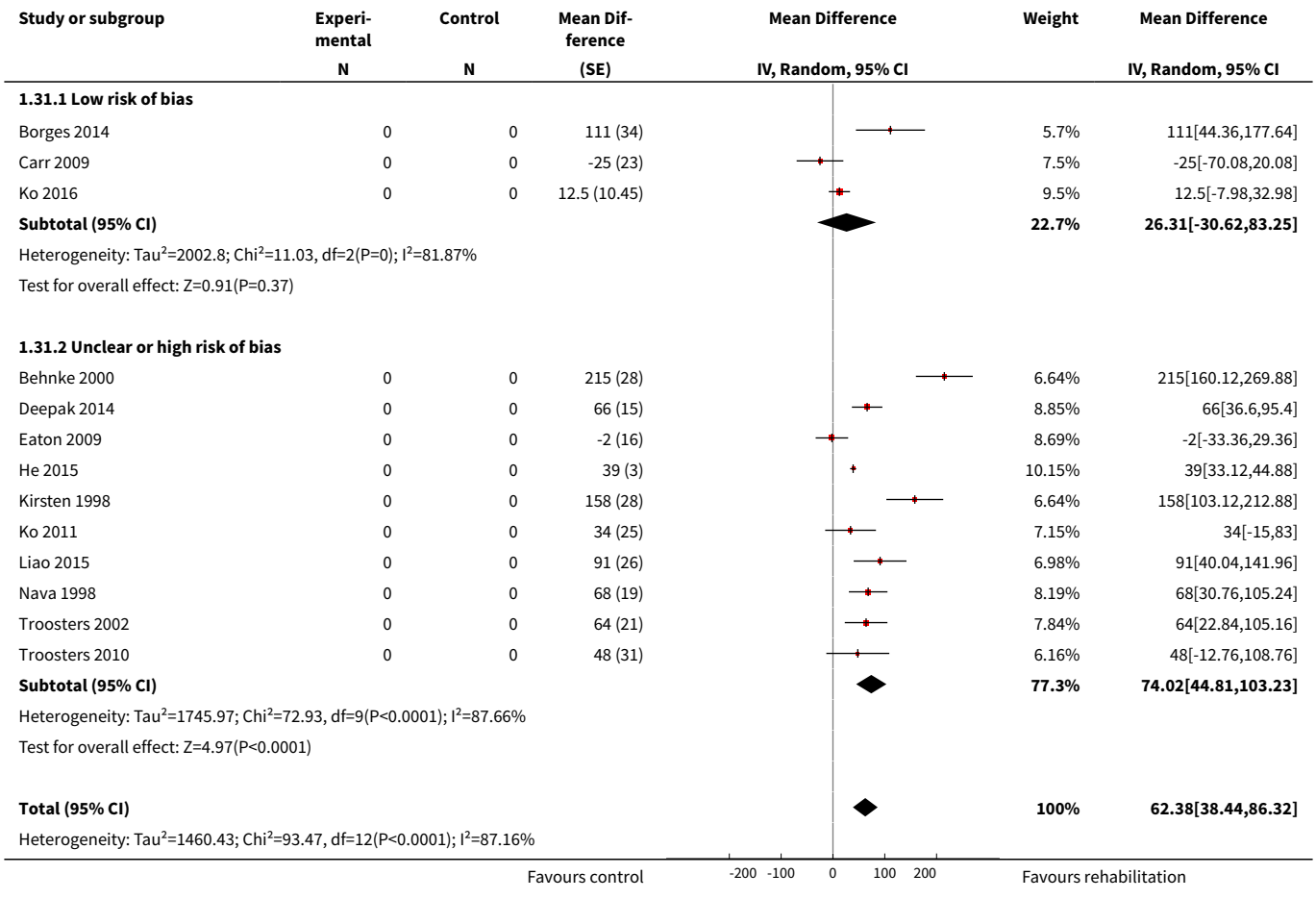


Analysis 1.31. Comparison 1 Rehabilitation versus control, Outcome 31 Subgroup analysis 6-minute walk test: blinding.



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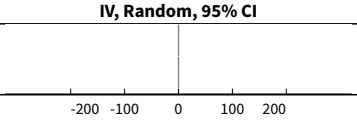
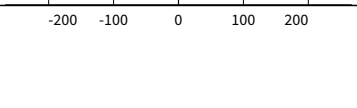
Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Test for overall effect: Z=5.11(P<0.0001)						
Test for subgroup differences: Chi^2=2.14, df=1 (P=0.14), I^2=53.16%						



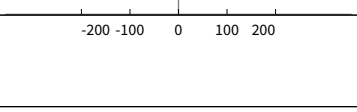
Analysis 1.32. Comparison 1 Rehabilitation versus control, Outcome 32 Subgroup analysis shuttle walk test: extensiveness of rehabilitation programme.

Study or subgroup	Rehabilitation N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.32.1 Extensive rehab programmes						
Man 2004	0	0	74 (21)		24.59%	74[32.84,115.16]
Seymour 2010	0	0	51 (14.54)		27.05%	51[22.5,79.5]
Subtotal (95% CI)					**51.64%**	**58.45[35.02,81.88]**
Heterogeneity: Tau^2=0; Chi^2=0.81, df=1(P=0.37); I^2=0%						
Test for overall effect: Z=4.89(P<0.0001)						
1.32.2 Less-extensive rehab programmes						
Greening 2014	0	0	-14 (13)		27.56%	-14[-39.48,11.48]
Murphy 2005	0	0	96 (30)		20.81%	96[37.2,154.8]
Subtotal (95% CI)					**48.36%**	**37.68[-69.92,145.28]**
Heterogeneity: Tau^2=5515.5; Chi^2=11.32, df=1(P=0); I^2=91.17%						
Test for overall effect: Z=0.69(P=0.49)						
Total (95% CI)					**100%**	**48.11[-0.74,96.95]**
Heterogeneity: Tau^2=2084.54; Chi^2=22.76, df=3(P<0.0001); I^2=86.82%						
Test for overall effect: Z=1.93(P=0.05)						
Test for subgroup differences: Chi^2=0.14, df=1 (P=0.71), I^2=0%						



Analysis 1.33. Comparison 1 Rehabilitation versus control, Outcome 33 Subgroup analysis shuttle walk test: length of follow-up.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.33.1 Follow-up >3 months						
Greening 2014	0	0	-14 (13)		27.57%	-14[-39.48,11.48]
Murphy 2005	0	0	96 (30)		20.88%	96[37.2,154.8]
Subtotal (95% CI)					**48.45%**	**37.68[-69.92,145.28]**
Heterogeneity: Tau^2=5515.5; Chi^2=11.32, df=1(P=0); I^2=91.17%						
Test for overall effect: Z=0.69(P=0.49)						
1.33.2 Follow-up ≤3 months						
Man 2004	0	0	74 (21)		24.64%	74[32.84,115.16]
Seymour 2010	0	0	51 (15)		26.91%	51[21.6,80.4]



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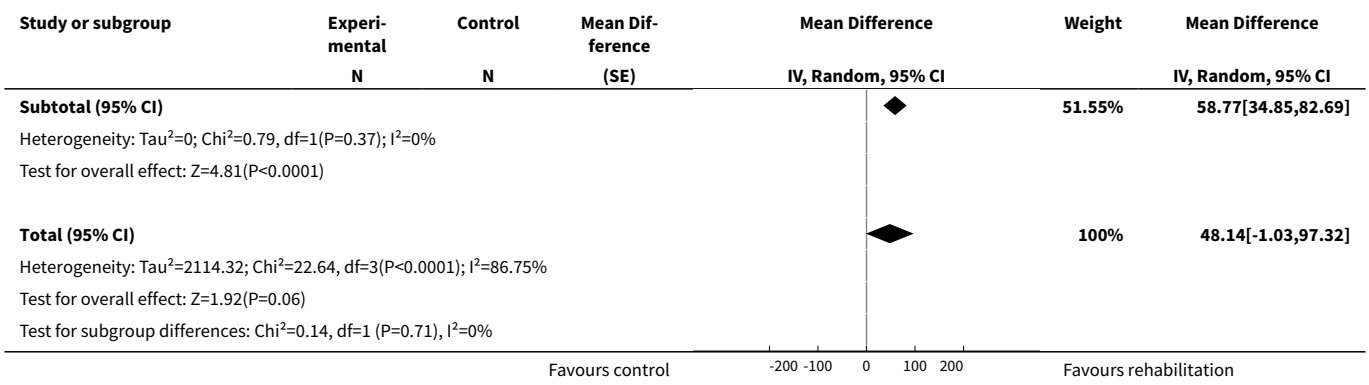
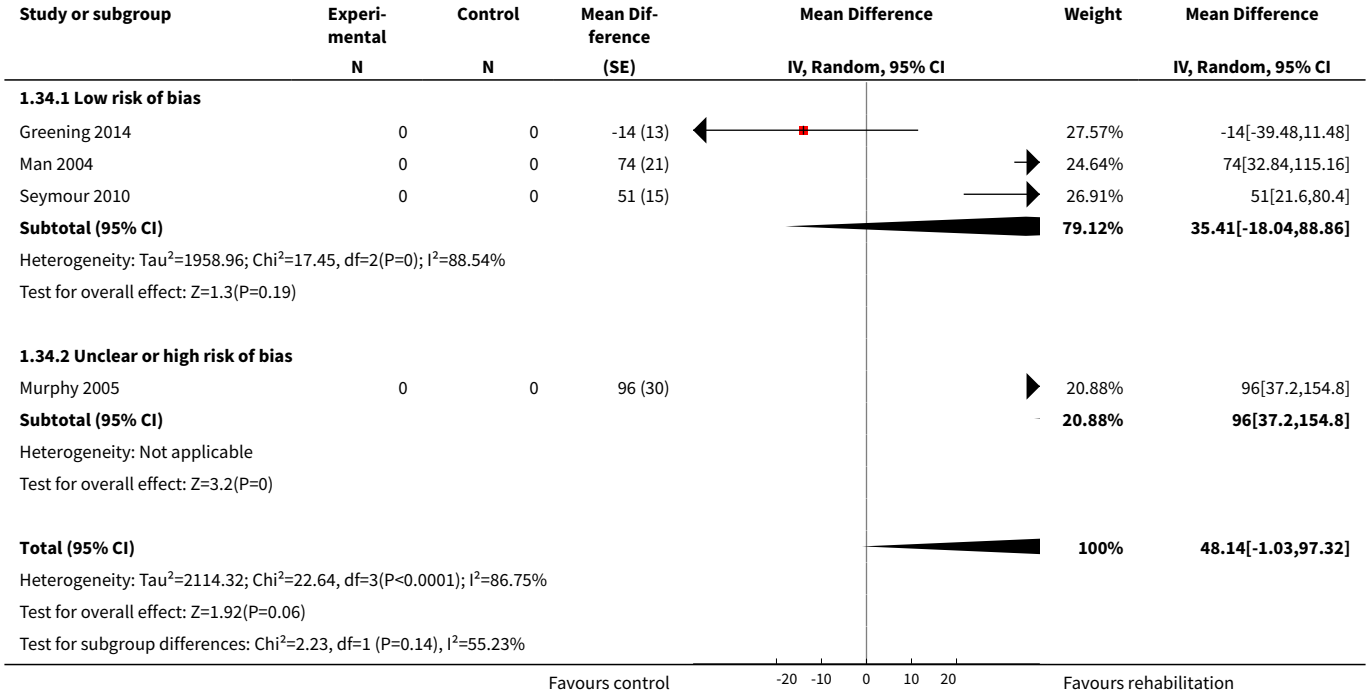
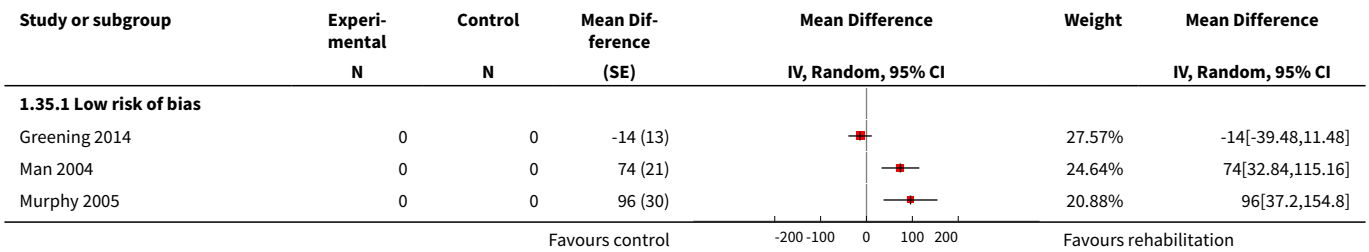


Analysis 1.34. Comparison 1 Rehabilitation versus control, Outcome 34 Subgroup analysis shuttle walk test: generation of random sequence.



Analysis 1.35. Comparison 1 Rehabilitation versus control, Outcome 35 Subgroup analysis shuttle walk test: concealment of random allocation.



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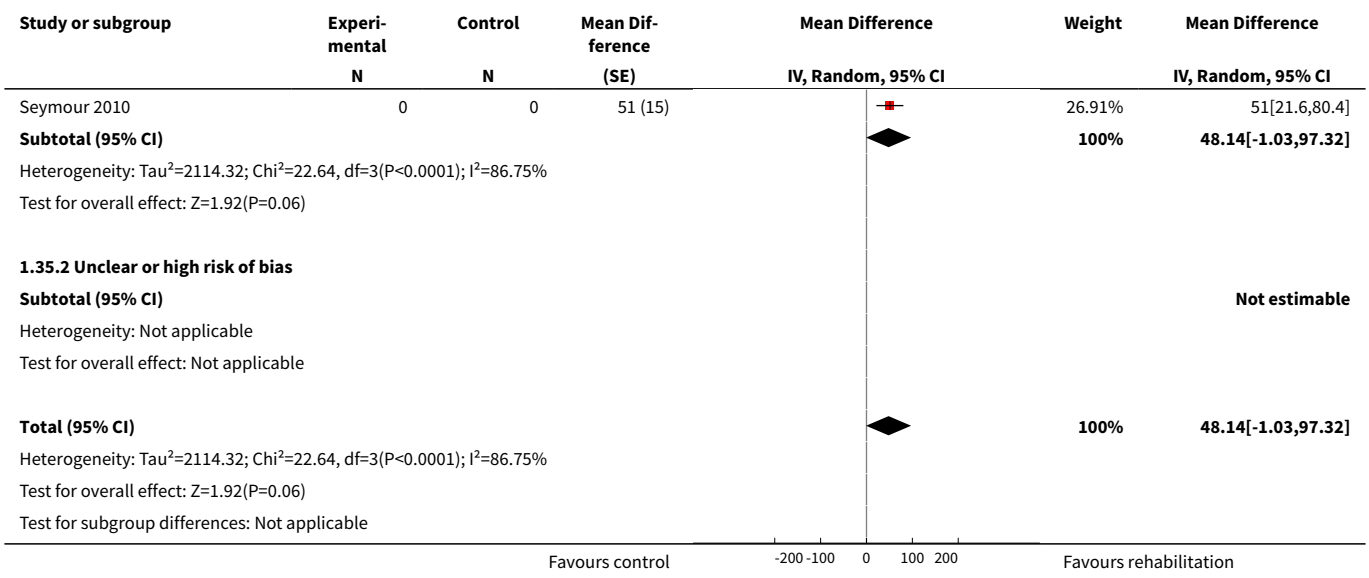
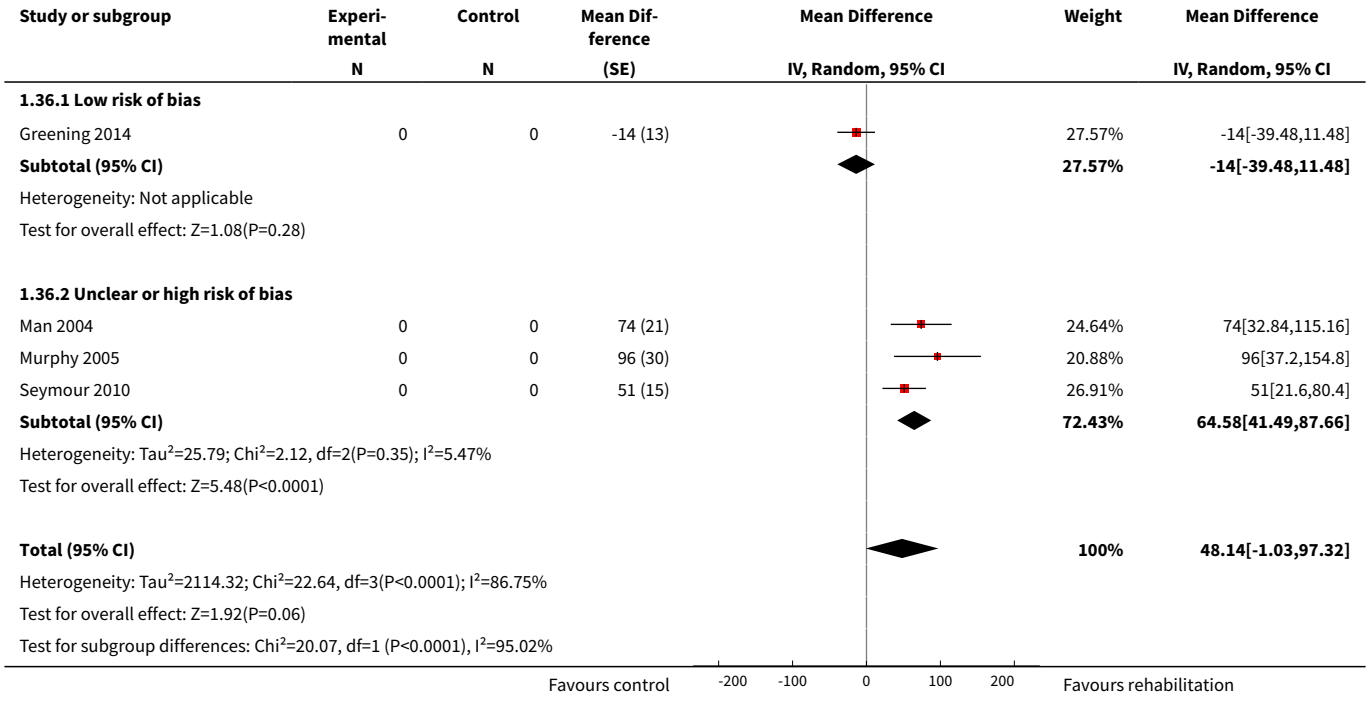


Analysis 1.36. Comparison 1 Rehabilitation versus control, Outcome 36 Subgroup analysis shuttle walk test: blinding.



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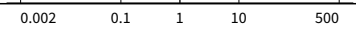
Analysis 1.37. Comparison 1 Rehabilitation versus control, Outcome 37 Hospital readmission (to end of follow-up) with separated new trial data.

Study or subgroup	Pulmonary rehab n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.37.1 Existing trials					
Behnke 2000	3/14	9/12		8.77%	0.09[0.01,0.56]
Eaton 2009	11/47	15/50		14.78%	0.71[0.29,1.77]
Man 2004	2/20	12/21		9.46%	0.08[0.02,0.45]
Murphy 2005	2/13	5/13		8.52%	0.29[0.04,1.9]
Seymour 2010	2/30	10/30		9.89%	0.14[0.03,0.72]
Subtotal (95% CI)	**124**	**126**		**51.41%**	**0.22[0.08,0.58]**
Total events: 20 (Pulmonary rehab), 51 (Control)					
Heterogeneity: Tau²=0.61; Chi²=8.15, df=4(P=0.09); I²=50.95%					
Test for overall effect: Z=3.06(P=0)					
1.37.2 New trials added					
Greening 2014	108/169	84/151		17.79%	1.41[0.9,2.21]
Ko 2011	16/30	13/30		13.96%	1.49[0.54,4.14]
Ko 2016	44/90	63/90		16.84%	0.41[0.22,0.76]
Subtotal (95% CI)	**289**	**271**		**48.59%**	**0.93[0.38,2.26]**
Total events: 168 (Pulmonary rehab), 160 (Control)					
Heterogeneity: Tau²=0.49; Chi²=11, df=2(P=0); I²=81.82%					
Test for overall effect: Z=0.16(P=0.87)					
Total (95% CI)	**413**	**397**		**100%**	**0.44[0.21,0.91]**
Total events: 188 (Pulmonary rehab), 211 (Control)					
Heterogeneity: Tau²=0.74; Chi²=29.8, df=7(P=0); I²=76.51%					
Test for overall effect: Z=2.2(P=0.03)					
Test for subgroup differences: Chi²=4.65, df=1 (P=0.03), I²=78.5%					



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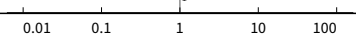
Analysis 1.38. Comparison 1 Rehabilitation versus control, Outcome 38 Mortality with separated new trial data.

Study or subgroup	Pulmonary rehab n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.38.1 Existing trials					
Behnke 2000	1/14	1/12		7.53%	0.85[0.05,15.16]
Man 2004	1/20	2/21		9.45%	0.5[0.04,5.99]
Troosters 2002	6/24	12/19		19.91%	0.19[0.05,0.72]
Subtotal (95% CI)	**58**	**52**		**36.89%**	**0.28[0.1,0.84]**
Total events: 8 (Pulmonary rehab), 15 (Control)					
Heterogeneity: Tau²=0; Chi²=1.07, df=2(P=0.59); I²=0%					
Test for overall effect: Z=2.29(P=0.02)					
1.38.2 New trials added					
Greening 2014	41/169	22/151		30.49%	1.88[1.06,3.33]
Ko 2011	0/30	2/30		6.79%	0.19[0.01,4.06]
Ko 2016	10/90	12/90		25.83%	0.81[0.33,1.99]
Subtotal (95% CI)	**289**	**271**		**63.11%**	**1.14[0.48,2.71]**



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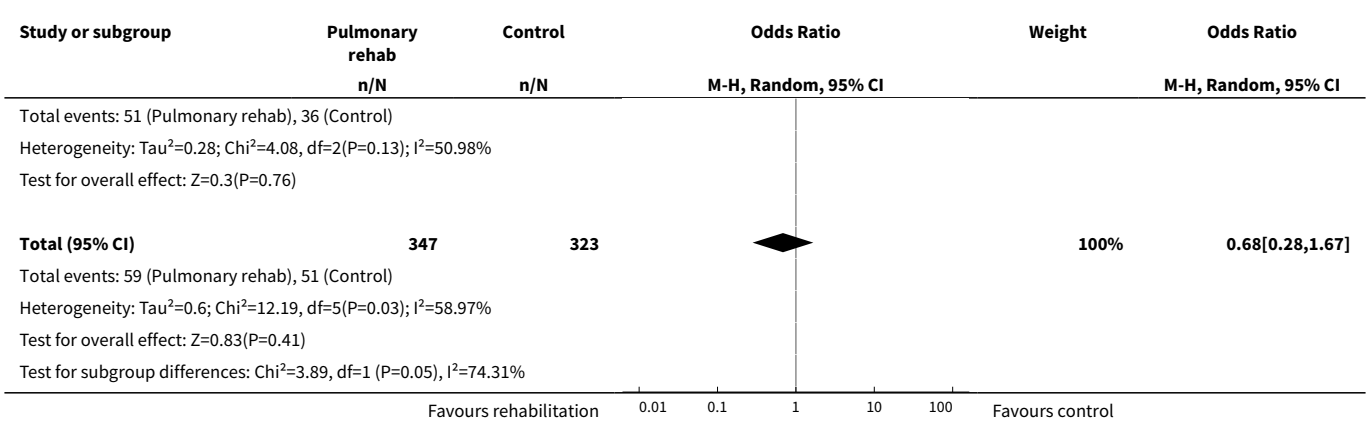
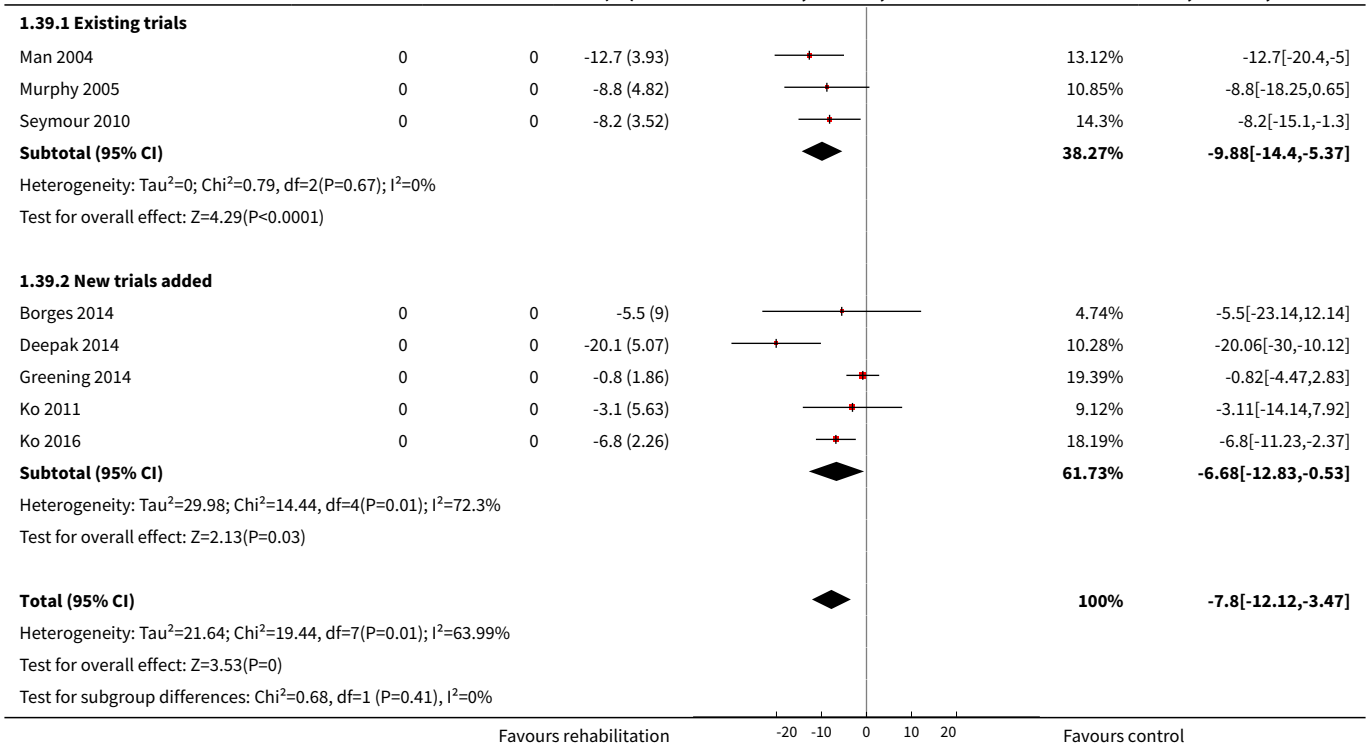


Analysis 1.39. Comparison 1 Rehabilitation versus control, Outcome 39 Health-related quality of life: SGRQ total with separated new trial data.



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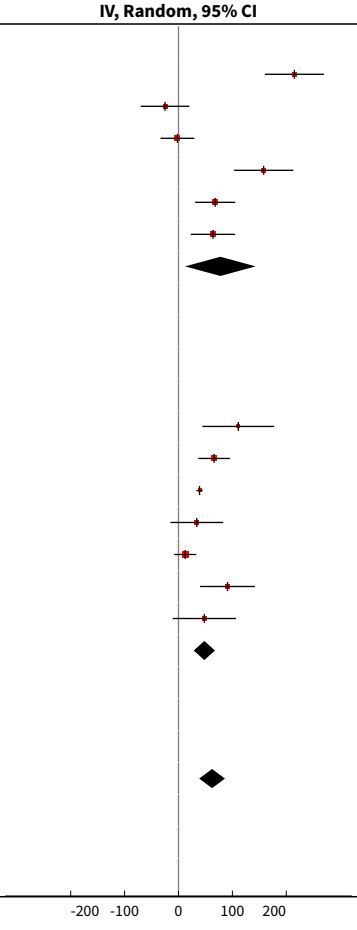
Analysis 1.40. Comparison 1 Rehabilitation versus control, Outcome 40 Change from baseline in 6 minute walking test with separated new trial data.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.40.1 Existing trials						
Behnke 2000	0	0	215 (28)		6.63%	215[160.12,269.88]
Carr 2009	0	0	-25 (23)		7.48%	-25[-70.08,20.08]
Eaton 2009	0	0	-2 (16)		8.68%	-2[-33.36,29.36]
Kirsten 1998	0	0	158 (28)		6.63%	158[103.12,212.88]
Nava 1998	0	0	68 (19)		8.18%	68[30.76,105.24]
Troosters 2002	0	0	64 (21)		7.83%	64[22.84,105.16]
Subtotal (95% CI)					**45.43%**	**77.7[12.21,143.2]**
Heterogeneity: Tau²=6179.55; Chi²=71.6, df=5(P<0.0001); I²=93.02%						
Test for overall effect: Z=2.33(P=0.02)						
1.40.2 New trials added						
Borges 2014	0	0	111 (34)		5.69%	111[44.36,177.64]
Deepak 2014	0	0	66 (15)		8.84%	66[36.6,95.4]
He 2015	0	0	39 (3)		10.14%	39[33.12,44.88]
Ko 2011	0	0	34 (25)		7.14%	34[-15,83]
Ko 2016	0	0	12.5 (10.45)		9.49%	12.5[-7.98,32.98]
Liao 2015	0	0	91 (26)		6.97%	91[40.04,141.96]
Troosters 2010	0	0	48 (30)		6.31%	48[-10.8,106.8]
Subtotal (95% CI)					**54.57%**	**48[28.32,67.68]**
Heterogeneity: Tau²=363.58; Chi²=18.28, df=6(P=0.01); I²=67.18%						
Test for overall effect: Z=4.78(P<0.0001)						
Total (95% CI)					**100%**	**62.35[38.45,86.25]**
Heterogeneity: Tau²=1457.56; Chi²=93.48, df=12(P<0.0001); I²=87.16%						
Test for overall effect: Z=5.11(P<0.0001)						
Test for subgroup differences: Chi²=0.72, df=1 (P=0.39), I²=0%						



ADDITIONAL TABLES

Table 1. Extensiveness of pulmonary rehabilitation programmes of included trials

Study	Number of sessions	Trainings per week	Rehabilitation programme	Supervision of training	Extent of rehabilitation programme
Behnke 2000	+1[a] (p 1185)	-	-	-1[b] (p 1185)	Extensive
Borges 2014	-2[c] (p 1642)	-	-1[d] (p 1639)	-	Not extensive
Carr 2009	-1[e] (p 320-1)	-	-	-	Moderately extensive
Deepak 2014	Unclear[f]	Unclear	-	-	Unclear
Eaton 2009	-2[c] (p 231-2)	-	+1[g] (p 231)	-	Moderately extensive

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Table 1. Extensiveness of pulmonary rehabilitation programmes of included trials *(Continued)*

Greening 2014	-	-	+1[g] (p 3)	-2[h] (p 3-4)	Moderately extensive
He 2015	-				Extensive
Kirsten 1998	-	-	-	-1[b] (p 1193)	Moderately extensive
Ko 2011	-	-	-	-	Extensive
Ko 2016	-	-	+1[g] (p 6)	-1[b] (p 7)	Extensive
Liao 2015	-2[c] (p 1706)	-	+1[g] (p 1705)	-	Moderately extensive
Man 2004	-	-	+1[f] (p 2)	-	Extensive
Murphy 2005	-1[e] (p 1298)	-	-	-	Moderately extensive
Nava 1998	+1[a] (p 850-1)	-	-	-	Extensive
Seymour 2010	-1[e] (p 423 & 425)	-	+1[f] (p 423)	-	Extensive
Tang 2012	-2[c] (p 164 & 167)	-	-	-	Slightly extensive
Torres-Sánchez 2014	Unclear	Unclear	Unclear	Unclear	Unclear
Torres-Sánchez 2015	-1[e] (p 3)	-	-	-	Moderately extensive
Troosters 2002	+1[a] (p 208-9)	-	-	-	Extensive
Troosters 2010	-2[c] (p 1073-4)	-	-1[d] (p 1073)	-	Not extensive

Explanations for downgrading and upgrading
[a](> 30 sessions).
[b]Some training sessions unsupervised.
[c]< 10 exercise training sessions.
[d]Only strength training.
[e]10 to 15 exercise training sessions.
[f]14 weeks, but unclear number of sessions per week.
[g]Comprehensive self-management training.
[h]Mostly unsupervised training (> 80% of all sessions).

APPENDICES

Appendix 1. Search methods up to October 2010

We performed literature searches in the following electronic databases:
MEDLINE
Embase
PEDro (Physiotherapy Evidence Database)
The Cochrane Central Register of Controlled Trials (CENTRAL; 2008, Issue 2)

We performed a very broad literature search to identify any randomised controlled studies on pulmonary rehabilitation in patients with COPD. The search strategy for MEDLINE and Embase can be found in Appendix 1. In addition, we used the PubMed "related articles" func-

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tion for included studies to identify further studies. Also, we performed a Science Citation Index search for studies that cite included studies, as well as for studies that are cited by included studies.

In addition, we carried out a search of the Cochrane Airways Review Group Specialised Register of COPD trials, using the following terms:

(rehabilitat* or fitness or exercis* or physical* or train* or kinesio* or endurance*) and (acute* or exacerb* or emerg* or hospital* or admit* or admis* or discharg*)

Combined search strategy for MEDLINE (Ovid) and Embase (Ovid)
1 lung diseases obstructive.af.
2 chronic obstructive lung disease.af.
3 chronic obstructive pulmonary disease.af.
4 exp pulmonary disease chronic obstructive/
5 or/1-4
6 rh.fs.
7 rehabilitation.de.
8 exp exercise movement techniques/
9 exp exercise test/
10 exp physical endurance/
11 exp muscle training/
12 exp kinesiotherapy/
13 exp exercise/
14 or/6-13
15 5 and 14
16 clinical trial.pt.
17 exp epidemiologic methods/
18 exp controlled study/
19 exp major clinical study/
20 exp evidence based medicine/
21 or/16-20
22 15 and 21
23 comment.pt.
24 editorial.pt.
25 exp editorial/
26 or/23-25
27 22 not 26
28 remove duplicates from 27

Appendix 2. Sources and search methods for the Cochrane Airways Review Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly

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(Continued)

AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

COPD search

1. Lung Diseases, Obstructive/

2. exp Pulmonary Disease, Chronic Obstructive/

3. emphysema$.mp.

4. (chronic$ adj3 bronchiti$).mp.

5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.

6. COPD.mp.

7. COAD.mp.

8. COBD.mp.

9. AECB.mp.

10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/

2. (randomized or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

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6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and the RCT filter are adapted to identify trials in other electronic databases.

Appendix 3. Search strategy to identify relevant trials from the CAGR for 2016 update

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All

#2 MeSH DESCRIPTOR Bronchitis, Chronic

#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)

#4 COPD:MISC1

#5 (COPD OR COAD OR COBD):TI,AB,KW

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 MeSH DESCRIPTOR Rehabilitation Explode All

#8 rehabilitat* or fitness or exercis* or physical* or train* or kinesio* or endurance*

#9 #7 or #8

#10 MeSH DESCRIPTOR Acute Disease

#11 MeSH DESCRIPTOR Disease Progression

#12 (acute* or exacerb* or emerg* or admit* or admis* or discharg*) or hospital*:ti,ab,kw

#13 #10 or #11 or #12

#14 #6 and #9 and #13

#15 (#14) AND (INREGISTER)

[Note: in field #4, MISC1 denotes the field in which the reference has been coded for condition, in this case, COPD.]

F E E D B A C K

Details of interventions administered in the studies, 6 July 2009

Summary

Thanks for a very helpful review. I am interested in using for my patients, but am puzzled by which program of "rehabilitation" to adopt. The table of characteristics shows considerable variation, with several combinations, although most seem to be endurance exercise only rather than a more complex "rehabilitation" program. I was interested in any advice on what program I should implement with my patients. Could this (and a sample program) be included with the updated review?

Reply

Thank you for this comment. Based on our review, we cannot make any statements about which rehabilitation programmes work best. However, there are systematic reviews on trials comparing different exercise programs that may help you defining your rehabilitation programme (e.g. Puhan et al. Comparison of exercise modalities and intensities to treat skeletal muscle dysfunction during respiratory rehabilitation in COPD patients - a systematic review. Thorax 2005;60(5):367-75).

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Contributors

Paul Glasziou

Use of data from Greening 2014 trial, 13 September 2019

Summary

Dear authorship team, I wish to comment on some ambiguities regarding the reporting of data from Greening 2014. This study has had an important impact on the field, hence accurate reporting of its findings is essential. I note the following ambiguities that I feel should be addressed:

1. The source of data are not currently clear. As the publicly available paper comprises patients with conditions other than COPD, one presumes the data reported in this review relate specifically to those patients with a diagnosis of COPD. Data related to most (but not all) outcomes for the COPD patient subset are unavailable in the original paper and its accompanying online supplement. If data were sourced directly from the authors for the purpose of this review, the study reference should be changed from its current label of 'published data only'.
2. It would be helpful for the authors to clarify which one of Greening's analyses was used as the source of data for this Cochrane review, as the paper describes outcome data from I) an intention-to-treat analysis; ii) a per protocol analysis; and iii) a customised sub-analysis of participants who were not readmitted during the follow-up period.
3. Is there a data entry error related to the subgroup analyses related to this study by Greening and colleagues? I note, for example, that the outcome of shuttle walk distance (presumably measured in metres) is reported in Analyses 1.32 to 1.35. I question whether the data reported in Analysis 1.32 are correct, as it is the only analysis that demonstrates a different effect estimate for this individual study (MD -19.00; 95% CI-44.48 to 6.48) and the overall outcome (MD 47.10; 95% CI -4.53 to 98.74), compared to Analyses 1.33 to 1.35 (Greening 2014, MD -14.00; 95% CI -39.48 to 11.48) and overall outcome (MD 48.14; 95% CI -1.03 to 97.32). The nature of the different subgroup analyses (intervention extensiveness, length of follow-up, random sequence, allocation concealment, blinding) should not account for this difference. While I don't feel these changes will significantly alter the implications of this review, I feel this amendment is important as other clinicians and researchers may look to this Cochrane review (as I did) to identify the data that are not publicly available in the Greening paper. Many thanks for considering these comments.

Christain Osadnik, Department of Physiotherapy, Monash University, Melbourne Victoria, Australia

Do you have any affiliation with or involvement in any organisation with a financial interest in the subject matter of your comment?: No

Reply

Thank you for the feedback and the opportunity to add clarity to the review.

1. We received the data (aggregated) for COPD patients only from Greening et al. We have changed the reference as requested and noted this in the text of the review.
2. For the readmission and mortality outcomes we used ITT (as far as we understood when getting the data, but there was an imbalance in numbers, with 169 participants with COPD in the intervention group and 151 participants with COPD in the control group) and for ISWT and SGRQ we received ITT data. But since some participants withdrew or died, these did not match up to those randomized. We did not get the IPD and other variables to allow us to do any imputation procedures to deal with imbalance. Therefore the analyses are ITT with some missing data.
3. There is a mistake in the Analysis 1.32. The correct value is -14 instead of -19. All the analysis (1.6, and 1.33-1.35) we used -14 for the difference in the ISWT. We updated analysis Analysis 1.32 with the correct value. This resulted in a small, but unimportant, change in the total analysis result from (MD 47.10; 95% CI -4.53 to 98.74) to (MD 48.11, 95% CI -0.74 to 96.95).

Contributors

Feeddback submitter: Christian Osadnik

Feedback Editor: Sally Spencer

Authors: Milo Puhan, Elena Gimeno, Chris Cates, Thierry Troosters.

WHAT'S NEW

Date	Event	Description
18 November 2019	Feedback has been incorporated	We provided the information that we received the ITT data for COPD patients only from the authors of Greening 2014.

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Date	Event	Description
		In analysis 1.32, we corrected a mistake: We now use, as in all other analyses, the correct between group difference on -14 instead of -19. The results did not change materially.

HISTORY

Protocol first published: Issue 2, 2005
Review first published: Issue 1, 2009

Date	Event	Description
20 October 2015	New citation required and conclusions have changed	Analyses were stratified for how extensive rehabilitation programmes were because they differed substantially. The impact of new evidence on patient-important outcomes gathered for this review update is emphasised in the revised abstract and review.
20 October 2015	New search has been performed	This review updates the review published in 2010. We ran a search on 8 October 2014, and again on 20 October 2015, and ran handsearches up to 5 April 2016. This update identified 11 additional studies (Borges 2014; Deepak 2014; Greening 2014; He 2015; Ko 2011; Tang 2012; Torres-Sánchez 2014; Torres-Sánchez 2015; Troosters 2010; Ko 2016; Liao 2015) that added 1045 participants. We included in this update a 'Summary of findings' table that was based on GRADE and revised the Discussion section substantially because additional evidence became available.
10 August 2011	New citation required but conclusions have not changed	This review has been published as a new citation version to correct an error by which we omitted this at the last update. We changed the review author byline at the last update.
12 July 2010	New search has been performed	We incorporated posted comments into the review. We ran a new literature search and included 3 new studies (Eaton 2009; Carr 2009; Seymour 2010), increasing the total number of participants from 219 to 432. We made no changes to the review conclusions.
8 April 2008	Amended	We converted the review to new review format.
20 February 2005	New citation required and major changes	We made substantive amendments.

CONTRIBUTIONS OF AUTHORS

Protocol writing: Puhan, Scharplatz, Gimeno-Santos.
Acquisition of data: Puhan, Gimeno-Santos, Scharplatz.
Analysis and interpretation of data: Puhan, Gimeno-Santos, Scharplatz, Troosters, Cates.
Drafting of manuscript: Puhan.
Critical revision of manuscript for important intellectual content: Puhan, Gimeno-Santos, Scharplatz, Troosters, Cates.

Dr Madlaina Scharplatz (MS) and helped with the previous version of this review, but is not an author of the current version of the review.

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We thank Prof Johann Steurer and Prof Haydn Walters for contributions to previous versions.

DECLARATIONS OF INTEREST

MA Puhan, E Gimeno-Santos, CJ Cates: no conflicts of interest to declare.

T Troosters conducts research in this field and recruits participants with acute exacerbations into rehabilitation programmes.

SOURCES OF SUPPORT

Internal sources

- The review authors declare that no internal funding was received for this systematic review, Other.

External sources

- The study authors declare that no external funding was received for this systematic review, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Review authors added risk of bias tables for the 2010 update of this review. We added a 'Summary of findings' table, along with specified subgroup analyses on extensiveness of pulmonary rehabilitation programmes, length of follow-up and three indicators of methodological quality.

We added clarification regarding types of studies: We did not include studies on pulmonary rehabilitation programmes that included only neuromuscular stimulation or inspiratory muscle training but no physical exercise programme.

In the original protocol, we planned to attempt to obtain data from intention-to-treat (ITT) and per-protocol populations, and to perform a sensitivity analysis to see whether this made a difference in meta-analysis results; however, the number of trials and the quality of their reporting did not allow us to compare ITT and per-protocol analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

*Exercise Tolerance; Disease Progression; Health Status; Hospitalization [*statistics & numerical data]; Patient Readmission [statistics & numerical data]; Pulmonary Disease, Chronic Obstructive [mortality] [*rehabilitation]; Quality of Life; Randomized Controlled Trials as Topic; Resistance Training [methods]

MeSH check words

Humans

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